



No. 09-093300-00003-0000

Fecha: 2011-01-18 12:14:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 77

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Número del expediente: 09 93300

Solicitante: DAIICHI SANKYO COMPANY LIMITED UBE INDUSTRIES LTDA.

Apoderado: LUZ CLEMENCIA SUAREZ DE PAEZ

Título de la nueva creación o denominación del signo: "METODO PARA LA PRODUCCION DE CLORHIDRATO DE PRASUGREL DE LATA PUREZA"

Gaceta: 621

③

OPOSICIÓN PRESENTADA POR:

		IDENTIFICACIÓN
SOLICITANTE	Nombre: <u>LABORATORIOS SYNTHESIS S.A.S.</u>	
	Dirección: <u>CARRERA 44 N° 20C 73</u>	C.C. ☐ NIT ☒
	Nacionalidad o Domicilio: <u>COLOMBIA</u> Lugar de Constitución: <u>BOGOTA</u>	C.E. ☐ Otro ☐
	Telefono: <u>3 69 22 22</u> Fax: _____ E-mail: _____	Cual _____ Número <u>860.000.760-1</u>
REPRESENTANTE O APODERADO	Nombre: <u>ELIANA ISaura MORENO BOHORQUEZ</u>	
	Dirección: <u>CARRERA 13 No. 119-95</u>	C.C. ☒ NIT ☐
	Telefono: <u>(571)213 12 13</u> Fax: <u>(571)612 19 79</u> E-mail: <u>negocios@optimum-co.com</u>	C.E. ☐ Otro ☐
		Cual _____ Número <u>51'975.664 TP.83823</u>

④

FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____ Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHÓRQUEZ

FIRMA: 

C.C. 51.975.664

TP. 83823

Señor Jefe,
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 09 93300
Asunto : Oposición a la solicitud de patente de Invención titulada
"METODO PARA LA PRODUCCION DE
CLORHIDRATO DE PRASUGREL DE LATA PUREZA"
Solicitantes : DAIICHI SANKYO COMPANY LIMITED Y UBE
INDUSTRIES LTDA.
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial
N° 621 del 20 de octubre de 2010

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. **83823** del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** Conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "METODO PARA LA PRODUCCION DE CLORHIDRATO DE PRASUGREL DE LATA PUREZA", cuyos titulares son **DAIICHI SANKYO**

COMPANY LIMITED Y UBE INDUSTRIES LTDA., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

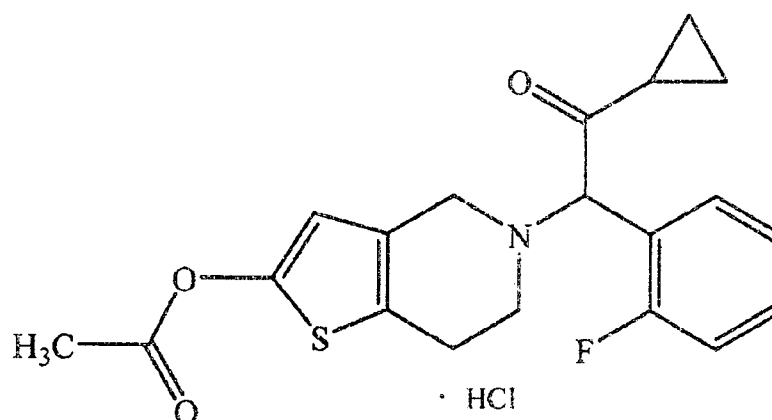
1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular PRASUGREL. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 02 de septiembre de 2009 reivindicando prioridad bajo la solicitud JP20070053093 del 2007-03-02; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010, cuya publicación internacional corresponde a la WO2008108291 del 2008-09-12.

2.2. La solicitud colombiana 09 93300 objeto de la presente oposición es proveer clorhidrato de prasugrel con un contenido reducido de CATP, y lo similar. (ver fórmula (1) En donde el método para producir clorhidrato de prasugrel representado por la fórmula anterior, es caracterizado porque comprende, en la etapa (i), controlar, a valores bajos, la temperatura durante la adición, opcionalmente a gotas, de un agente de cloración y la temperatura de reacción después de la adición, opcionalmente a gotas, del agente de cloración.



Formula 1

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: “Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”, tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: US5288726 publicada el 22 de febrero de 1994.
- D2: US5874581 publicada el 23 de febrero de 1999.



2.4. Ahora bien, el documento D1, se refiere a una serie de nuevos derivados de tetrahidrotieno[3,2-c] piridina y análogos furo y pirrol de estos derivados, y proporciona los procedimientos para preparar estos derivados así como los métodos y las composiciones que los utilizan para inhibir la agregación de las plaquetas de la sangre, y, en concreto para el tratamiento y la profilaxis de las trombosis y las embolias. Dicho documento D1 revela la preparación de prasugrel de forma libre en donde, OXTP se utiliza como subproducto. Finalmente el documento D1 indica de forma particular en la descripción que los compuestos de post-reacción pueden ser purificados a través de re cristalización y que la re cristalización es un método de purificación de compuestos común.

2.5. El documento D2 por su parte revela la preparación de prasugrel de forma libre, y un método similar al de la solicitud colombiana objeto de la presente oposición, en donde se utilizan subproductos como OXTP, (o CATP), teniendo en cuenta temperaturas; así mismo dicho documento D2 revela la obtención de prasugrel de forma libre donde el método de reacción en la reacción de la invención puede ser un método común y un método de la adición de un reactivo de reacción, etc., no son particularmente limitados. El aislamiento del compuesto deseado de la mezcla de reacción según el mismo documento D2, puede ser llevado a cabo por la operación común, pero teniendo en cuenta las propiedades físicas del compuesto deseado, cristalización, extracción, lavado, columna de cromatografía, etc., y pueden combinarse.

2.6. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir de dicho documento D1

por sí solo, o en combinación con D2 teniendo en cuenta que la formación de clorhidrato de prasugrel disolviendo el prasugrel purificado de forma libre obtenido, agregando opcionalmente a gotas un agente de cloración y la purificación de residuos y/o subproductos como OXTP o CATP por cristalización o re-cristalización son bien conocidas, proveer clorhidrato de prasugrel con un contenido reducido de un subproducto como CATP, o similares, que comprende, en la etapa (i), controlar, a valores bajos, la temperatura durante la adición, opcionalmente a gotas, de un agente de cloración y la temperatura de reacción después de la adición, opcionalmente a gotas, del agente de cloración. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 93300 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“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.”*. A la fecha de prioridad, 02 de marzo de 2007, a partir del documento D1 por sí solo, o en combinación con D2 teniendo en cuenta que la formación de clorhidrato de prasugrel disolviendo el prasugrel purificado de forma libre obtenido, agregando opcionalmente a gotas un agente de cloración y la purificación de residuos y/o subproductos como

OXTP o CATP por cristalización o re-cristalización son bien conocidas, proveer clorhidrato de prasugrel con un contenido reducido de un subproducto como CATP, o similares, caracterizado porque comprende, en la etapa (i), controlar, a valores bajos, la temperatura durante la adición, opcionalmente a gotas, de un agente de cloración y la temperatura de reacción después de la adición, opcionalmente a gotas, del agente de cloración; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“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.”*. La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **“METODO PARA LA PRODUCCION DE CLORHIDRATO DE PRASUGREL DE LATA PUREZA”**, cuyos titulares son **DAIICHI SANKYO COMPANY LIMITED Y UBE INDUSTRIES LTDA.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 621 del 20 de octubre de 2010.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US5288726 publicada el 22 de febrero de 1994.
- D2: US5874581 publicada el 23 de febrero de 1999.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

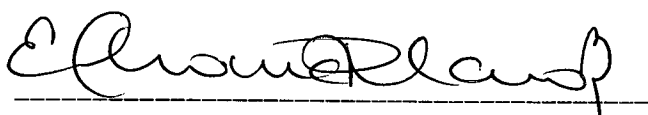
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US5288726 publicada el 22 de febrero de 1994.
 - D2: US5874581 publicada el 23 de febrero de 1999.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



Law

DILIGENCIA DE RECONOCIMIENTO REPUBLICA DE COLOMBIA

Compareció ante el Notario 18 del Circulo de Bogotá, ALBERTO PALACIOS quien exhibió la C. E 319788 Expedida en BOGOTÁ y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

17 ENE 2011

BOGOTÁ, D.C.

FIRMA

EL NOTARIO

HUELLA DEL INDICE DERECHO

18 NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTÁ D.C. 18 LA HUELLA SE AUTENTICA POR SIGNIFICADO INTERESADO

REPUBLICA DE COLOMBIA

ALBERTO VARGAS SALLO

NOTARIO 16 (E) DEL CIRCULO DE BOGOTÁ D.C.

CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

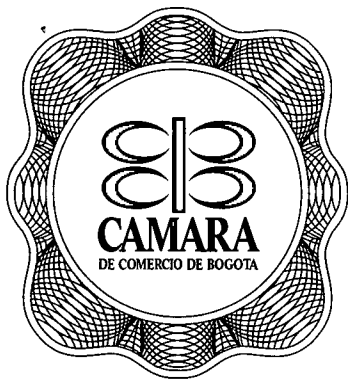
CERTIFICA:

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987	1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579
9244	23-XII- 1991	1 STAFE.BTA.	8-I -1.992 NO.351.255
8145	15- X - 1992	1 STAFE.BTA.	16- X-1.992 NO.382.488
1374	26- III-1993	1 STAFE.BTA.	19- III-1993 NO.399972
3120	01-VI-1.995	1A.STAFE BTA	23-VI- 1.995 NO.498.060
5435	17-IX-1.996	1A.STAFE BTA	30-IX- 1.996 NO.556.909
5435	17-IX-1.996	1A.STAFE BTA	01- X- 1.996 NO.557.146
5435	17-IX-1.996	1A.STAFE BTA	02- X- 1.996 NO.557.301
5942	7-X -1.996	1A.STAFE BTA	11- X- 1.996 NO.558.222
6305	24-X--1.996	1A.STAFE BTA	07-XI--1.996 NO.561.207
6929	25-XI-1.996	1A.STAFE BTA	12-XII-1.996 NO.565.961
787	19-II-1.997	1A.STAFE BTA	25-II -1.997 NO.575.141



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CAMARA DE COMERCIO DE BOGOTA

SEDE CENTRO

14 DE ENERO DE 2011

HORA 10:58:20

R030239466

PAGINA: 2 de 5

* * * * *

1024

28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO. INSC.
0007110	1997/10/28	0001	BOGOTA D.C.	1997/11/06	00609204
0001896	1998/03/16	0001	BOGOTA D.C.	1998/04/01	00628368
0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANTAR Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER

CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

** CAPITAL AUTORIZADO **

VALOR : \$20,000,000,000.00
NO. DE ACCIONES : 20,000,000.00
VALOR NOMINAL : \$1,000.00

** CAPITAL SUSCRITO **

VALOR : \$17,207,141,000.00
NO. DE ACCIONES : 17,207,141.00
VALOR NOMINAL : \$1,000.00

** CAPITAL PAGADO **

VALOR : \$17,207,141,000.00
NO. DE ACCIONES : 17,207,141.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: GERENCIA LA CUAL SERÁ ASUMIDA POR UN GERENTE Y UN SUBGERENTE QUIENES TENDRÁN REPRESENTACIÓN LEGAL DE LA SOCIEDAD.

CERTIFICA:

** NOMBRAMIENTOS **

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO

C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

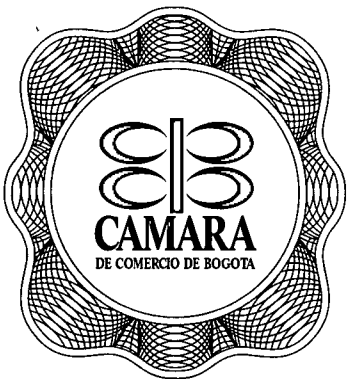
SUBGERENTE

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCTENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA



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CAMARA DE COMERCIO DE BOGOTA

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PAGINA: 3 de 5

* * * * *

DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

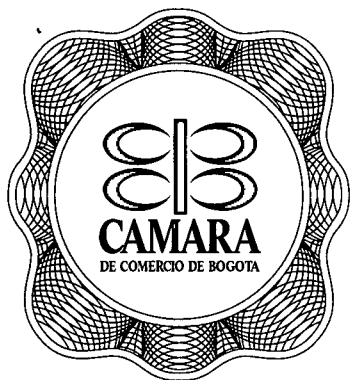
CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 654 DE LA NOTARIA 01 DE BOGOTA D.C., DEL 20 DE FEBRERO DE 2009, INSCRITA EL 02 DE MARZO DE 2009 BAJO EL NO. 15209 DEL LIBRO V, COMPARECIO ORLANDO MUÑOZ MARTINEZ IDENTIFICADO CON CEDULA DE CIUDADANIA NO. 8.317.044 EN SU CALIDAD DE DELEGADO GENERAL SUPLENTE DEL SÓCIO GESTOR LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL SEÑOR ANDRES FERNANDO MOLLAJOLI CENTURION, IDENTIFICADO CON CÉDULA DE EXTRANJERÍA NO. 351.283 QUE EN NOMBRE DE LA SOCIEDAD QUE REPRESENTO, ACTUÉ CON LAS MÁS AMPLIAS FACULTADES EN LA REPÚBLICA DE COLOMBIA, EN LOS SIGUIENTES ASUNTOS 1. PARTICIPAR EN CALIDAD DE SOCIO, ACCIONISTA O EMPRESARIO EN PERSONAS JURÍDICAS COLOMBIANAS, CONSTITUIDAS O POR CONSTITUIRSE, EN EL PORCENTAJE QUE LA APODERADA AQUÍ NOMBRADA ESTIME CONVENIENTE A NUESTROS INTERESES, CON FACULTAD PARA ENTREGAR LAS SUMAS CORRESPONDIENTES AL PAGO DEL MISMO; 2. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS; 3. REPRESENTAR A LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., EN LAS REUNIONES ASAMBLEA GENERAL O JUNTAS EN LAS CUALES TENGA INTERÉS; 4. EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRÉSTAMOS DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS, OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, Y NEGOCIAR EN GENERAL TÍTULOS VALORES Y RECIBIRLOS EN PAGO; 5. CELEBRAR ASÍ MISMO OPERACIONES RELACIONADAS CON LA PROTECCIÓN DE SUS BIENES, NEGOCIOS Y PERSONAS A SU SERVICIO; 6. CELEBRAR CONTRATOS DE CUENTAS EN

PARTICIPACIÓN, SEA COMO PARTICÍPE ACTIVA O COMO PARTICÍPE INACTIVA; 7. TRANSIGIR, DESISTIR Y APELAR DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES; 8. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. 9. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEA CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES; 10. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. 11. NOTIFICARSE VÁLIDAMENTE DE AQUELLOS ACTOS DEL ORDEN ADMINISTRATIVO O JUDICIAL QUE SE FORMULEN CONTRA LA SOCIEDAD, ASÍ CÓMO ABSOLVER INTERROGATORIOS CON CAPACIDAD PARA CONFESAR; 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A. 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SÍNTESIS LTDA. & CIA S.C.A., RECAUDAR O RECIBIR POR SUS FRUTOS Y CELEBRAR TODA CLASE DE CONTRATOS RELACIONADOS CON LA ADMINISTRACIÓN. 13. ENAJENAR, ADQUIRIR, PERMUTAR, GRAVAR, ARRENDAR BIENES MUEBLES, PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTIIESIS LTDA & CIA S.C.A, SIN LÍMITE DE CUANTIA. 14. ENAJENAR, PERMUTAR, ADQUIRIR, GRAVAR, ARRENDAR BIENES MUEBLES E INMUEBLES PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MAS ALTO EN LA FECHA DE CELEBRACIÓN Y TENGA RELACIÓN DIRECTA CON EL DESARROLLO SOCIAL, ASÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DE LA SOCIEDAD GESTORA. 15. TOMAR DINERO EN MUTUO, CON FACULTAD PARA ESTIPULAR TODO TIPO DE INTERESES, PLAZOS Y DEMÁS CONDICIONES Y CELEBRAR CONTRATOS DE CUENTA CORRIENTE; 16. GIRAR, ORDENAR GIRAR, ENDOSAR, PROTESTAR, OTORGAR, ACEPTAR ORDENAR AVALÚOS Y HACER TODA CLASE DE NEGOCIOS RELACIONADOS CON TÍTULOS VALORES CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MÁS ALTO EN LA FECHA DE SU CELEBRACIÓN, SÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DEL REPRESENTANTE LEGAL DE LA SOCIEDAD GESTORA. 17. PRESENTAR DECLARACIÓN DE RENTA, PATRIMONIO, IMPUESTOS A LAS VENTAS EN ADMINISTRACIÓN DE IMPUESTOS NACIONES Y MUNICIPALES E INTERPONER LOS RECURSOS Y DECLARACIONES PERTINENTES CONTRA ACTOS DE DICHA ADMINISTRACIÓN CON FACULTAD PARA DEFENDER LOS INTERESES DE LA SOCIEDAD EN ÉSTA MATERIA. 18. DESIGNAR APODERADO ESPECIAL PARA CADA PROCESO JUDICIAL O ADMINISTRATIVO. 19. PRÉSENTAR RECURSOS POR VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR 20. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES 21. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES 22. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE



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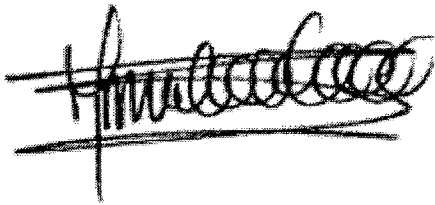
PAGINA: 4 de 5

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BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.308 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFienda LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F. SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G. OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS, RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR, RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR. I. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES.

VALOR : \$ 3,700

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

A handwritten signature in dark ink, appearing to be "H. Mulacae", is written over two horizontal lines. The signature is stylized and cursive.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

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Industria y Comercio

SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 004763

Bogotá D.C., 18 de 2011 - 11:28:31

RECIBIDO DE : LABORATORIOS SYNTHESIS LTDA & CIA S.C.A.

NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	396966916	17/01/2011	1.216.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNIDITARIO	Vr. CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	304.000.00	304.000.00
		12 MARCAS Y LEMAS COMERCIALES		\$304.000.00
			=====	=====

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-093300- -00003-0000

Fecha: 2011-01-18 12:14:22 Dep. 2020 DIR.NUEVASCR
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Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Linea: 018000-910165 Call Center: (571) 6513240

Enero 18 de 2011 - 11:28:31

United States Patent [19]

Koike et al.

US005288726A

[11] Patent Number: 5,288,726

[45] Date of Patent: Feb. 22, 1994

- [54] TETRAHYDROTHIENOPYRIDINE DERIVATIVES, FURO AND PYRROLO ANALOGS THEREOF AND THEIR PREPARATION AND USES FOR INHIBITING BLOOD PLATELET AGGREGATION

- [75] Inventors: Hiroyuki Koike; Fumitoshi Asai; Atsuhiko Sugidachi, all of Tokyo; Tomio Kimura, Ube; Teruhiko Inoue, Ube; Shigeyoshi Nishino, Ube; Yasunori Tsuzaki, Ube, all of Japan

- [73] Assignees: Ube Industries Limited, Ube; Sankyo Company, Limited, Tokyo, both of Japan

- [21] Appl. No.: 941,676

- [22] Filed: Sep. 8, 1992

- [30] Foreign Application Priority Data

Sep. 9, 1991 [JP]	Japan	3-227875
May 29, 1992 [JP]	Japan	4-138529

- [51] Int. Cl.⁵ A01K 3/14; C07D 513/04
 [52] U.S. Cl. 514/301; 546/114
 [58] Field of Search 546/114, 116; 514/301, 514/302

- [56] References Cited

U.S. PATENT DOCUMENTS

4,051,141	9/1977	Castaigne	260/294.8
4,075,215	2/1978	Castaigne	260/294.8
4,127,580	11/1978	Braye	546/114
4,136,186	1/1979	Frehel et al.	546/114
4,458,074	7/1984	Bouscuet et al.	546/114
4,464,377	8/1984	Blanchard et al.	424/256
4,529,596	7/1985	Aubert et al.	514/231
4,740,510	4/1988	Badorc et al.	514/291

FOREIGN PATENT DOCUMENTS

421861 4/1991 European Pat. Off. 546/114

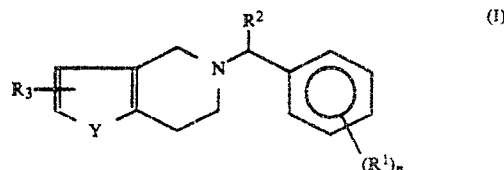
Primary Examiner—Alan L. Rotman

Assistant Examiner—Phyllis G. Spivack

Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

[57] ABSTRACT

Compounds of formula (I):



wherein: R¹ is hydrogen, alkyl, halogen, haloalkyl, hydroxy, alkoxy, haloalkoxy, alkylthio, haloalkylthio, amino, alkanoyl, haloalkanoyl, carboxy, alkoxycarbonyl, carbamoyl, cyano, nitro, alkanesulfonyl, haloalkanesulfonyl or sulfamoyl; R² is optionally substituted alkanoyl, optionally substituted alkenoyl, optionally substituted cycloalkylcarbonyl, substituted benzoyl, or 5,6-dihydro-1,4,2-dioxazin-3-yl; R³ is hydrogen, hydroxy, optionally substituted alkoxy, aralkyloxy, alkanoyloxy, alkenoyloxy, cycloalkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aralkyloxy carbonyloxy, phthalidylloxy, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy, (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy, optionally substituted amino or nitro; Y is —NH— or oxygen or sulfur; n is 1 to 5; and tautomers and salts of said compounds of formula (I), have the ability to inhibit blood platelet aggregation, and can thus be used for treatment and prophylaxis of thrombosis and embolisms.

56 Claims, No Drawings

**TETRAHYDROTHIENOPYRIDINE
DERIVATIVES, FURO AND PYRROLO ANALOGS
THEREOF AND THEIR PREPARATION AND
USES FOR INHIBITING BLOOD PLATELET
AGGREGATION**

BACKGROUND OF THE INVENTION

The present invention relates to a series of new tetrahydrothieno[3,2-c]pyridine derivatives and furo and pyrrolo analogs of these derivatives, and provides processes for preparing these derivatives as well as methods and compositions using them for inhibiting blood platelet aggregation.

A number of tetrahydrothienopyridine and tetrahydrofurofuryl derivatives is known, and some of these have been disclosed to have the ability to inhibit blood platelet aggregation. For example, U.S. Pat. Nos. 4,051,141, 4,075,215, 4,127,580, 4,464,377 and 4,529,596 all disclose compounds of this type, although not all disclose them for the inhibition of blood platelet aggregation. The closest prior art is believed to be U.S. Pat. No. 4,051,141, which discloses, inter alia, 5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and U.S. Pat. No. 4,529,596, which discloses, inter alia, 5-(2-chloro- α -methoxycarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

However, there are problems with the prior art compounds referred to above, especially in that many of them require a long time after administration before they manifest their activity. Accordingly, there is a need for new compounds of this type having improved activity and the ability to act faster.

We have now discovered a series of new tetrahydrothieno[3,2-c]pyridine derivatives and furo and pyrrolo analogs of these derivatives which have an improved ability to inhibit the aggregation of blood platelets.

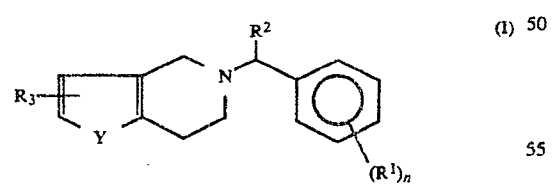
BRIEF SUMMARY OF INVENTION

It is, therefore, an object of the present invention to provide a series of new compounds of this type.

It is a further, and more specific object of the present invention to provide such compounds having valuable inhibitory activity against platelet aggregation.

Other objects and advantages of the present invention will become apparent as the description proceeds.

The compounds of the present invention are those compounds of formula (I):



wherein:

R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an alkanoyl

group having from 1 to 5 carbon atoms, a haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 1 to 10 carbon atoms, a substituted alkanoyl group which has from 2 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below, an alkenoyl group having from 3 to 6 carbon atoms, a substituted alkenoyl group which has from 3 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below, a cycloalkylcarbonyl group having from 4 to 8 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 8 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below, a substituted benzoyl group having at least one substituent selected from the group consisting of substituents B, defined below, or a 5,6-dihydro 1,4,2-dioxazin-3-yl group;

R³ represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a substituted alkoxy group which has from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents C, defined below, an aralkyloxy group in which the aralkyl part is as defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having from 3 to 6 carbon atoms, a cycloalkyl carbonyloxy group having from 4 to 8 carbon atom, an arylcarbonyloxy group in which the aryl part is as defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, an aralkyloxycarbonyloxy group in which the aralkyl part is as defined below, a phthalidylloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula -NR^aR^b

wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one substituent selected from the group consisting of substituents C, defined below,

an aralkylamino group in which the aralkyl part is as defined below, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having from 3 to 6 carbon atoms, a cycloalkylcarbonylamino group having from 4 to 8 carbon atoms, an arylcarbonylamino group in which the aryl part is as defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms, an aralkyloxycarbonylamino group in which the aralkyl part is as defined below, a phthalidylamino group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylamino group, a (5-phenyl-2-

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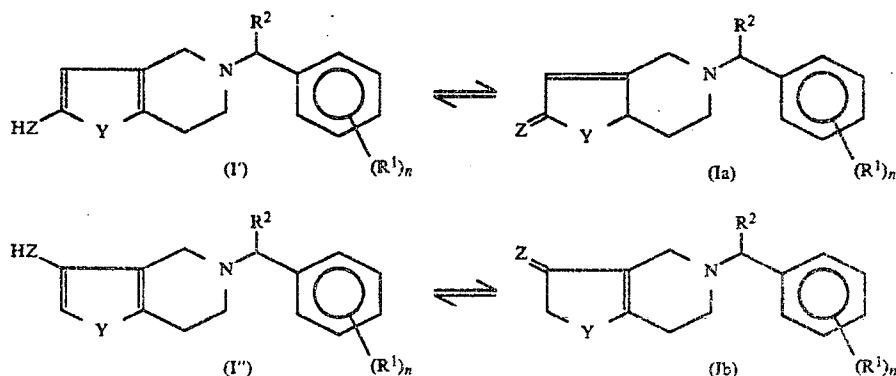
oxo-1,3-dioxolen-4-yl)methylamino group or a nitro group;
 Y represents a group of formula —NH— or an oxygen or sulfur atom; and
 n is an integer from 1 to 5, and, when n is an integer from 2 to 5, the groups represented by R¹ may be the same as or different from each other;
 said substituents A are selected from the group consisting of halogen atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms and cyano

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The invention also provides processes for preparing these compounds, which are described in greater detail hereafter.

DETAILED DESCRIPTION OF INVENTION

When the compounds of the present invention have an amino or hydroxy group at the 2- or 3- position (i.e. R³ represents an amino or hydroxy group at the 2- or 3- position), they can exist as keto-enol tautomers, that is:



groups;
 said substituents B are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms;
 said substituents C are selected from the group consisting of alkoxy groups having from 1 to 4 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms and arylcarbonyloxy groups in which the aryl part is as defined below;
 said aralkyl parts of said aralkyloxy, aralkyloxy, carbonyloxy, aralkylamino and aralkyloxycarbonylamino groups are alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one aryl group as defined below;
 said aryl groups and said aryl parts of said arylcarbonyloxy groups and of said arylcarbonylamino groups have from 6 to 10 carbon atoms in a carbocyclic ring which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D, defined below; and
 said substituents D are selected from the group consisting of the groups and atoms defined above in relation to R¹, other than said hydrogen atom; and tautomers thereof and pharmaceutically acceptable salts of said compounds of formula (I) and of said tautomers.

The invention also provides a pharmaceutical composition for the treatment and prophylaxis of thrombosis or embolisms, comprising an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof.

The invention still further provides a method for the treatment or prophylaxis of thrombosis or embolisms, comprising administering to a mammal, which may be human, an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof.

wherein Y, R¹, R² and n are as defined above, and Z represents a group of formula =NH or an oxygen atom. These tautomers may or may not be readily separable, and, if separable, may be separated by methods well known in the art. In any event, the present invention embraces both the individual isolated tautomers, as well as mixtures thereof, and both the isolated tautomers and such mixtures may be used in the compositions and methods of the present invention. In particular, the tautomers of formula (Ia) are preferred.

In the compounds of the present invention, where R¹ represents an alkyl group, this may be a straight or branched chain alkyl group having from 1 to 4 carbon atoms, and examples include the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and t-butyl groups. Of these, we prefer those alkyl groups having from 1 to 3 carbon atoms, more preferably the methyl and ethyl groups.

Where R¹ represents a halogen atom, this may be, for example, a fluorine, chlorine, iodine or bromine atom, and is preferably a fluorine or chlorine atom.

Where R¹ represents a haloalkyl group, the alkyl part may be any one of the alkyl groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkyl group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-iodoethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2-fluoropropyl, 3-fluoropropyl, 3-chloropropyl, 2-fluorobutyl, 3-fluorobutyl, 4-chlorobutyl and 4-fluorobutyl groups. The fluorine-substituted and chlorine-substituted groups are preferred, the fluorine-substituted groups being more preferred. The fluoromethyl, difluoromethyl and trifluoromethyl

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groups are most preferred, especially the trifluoromethyl group.

Where R^1 represents an alkoxy group, this may be a straight or branched chain alkoxy group having from 1 to 4 carbon atoms, and examples include the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and t-butoxy groups. Of these, we prefer those alkoxy groups having from 1 to 3 carbon atoms, more preferably the methoxy and ethoxy groups.

Where R^1 represents a haloalkoxy group, the alkoxy part may be any one of the alkoxy groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkoxy group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 2-iodoethoxy, 2,2,2-trichloroethoxy, 2,2,2-trifluoroethoxy, 2-fluoropropoxy, 3-fluoropropoxy, 3-chloropropoxy, 2-fluorobutoxy, 3-fluorobutoxy, 4-chlorobutoxy and 4-fluorobutoxy groups. The fluoroalkoxy groups are preferred. The fluoromethoxy, difluoromethoxy and trifluoromethoxy groups are most preferred, especially the trifluoromethoxy group.

Where R^1 represents an alkylthio group, this may be a straight or branched chain alkylthio group having from 1 to 4 carbon atoms, and examples include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio and t-butylthio groups. Of these, we prefer those alkylthio groups having from 1 to 3 carbon atoms, more preferably the methylthio and ethylthio groups.

Where R^1 represents a haloalkylthio group, the alkylthio part may be any one of the alkylthio groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkylthio group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethylthio, difluoromethylthio, trifluoromethylthio, 2-fluoroethylthio, 2-chloroethylthio, 2-bromoethylthio, 2-iodoethylthio, 2,2,2-trichloroethylthio, 2,2,2-trifluoroethylthio, 2-fluoropropylthio, 3-fluoropropylthio, 3-chloropropylthio, 2-fluorobutylthio, 3-fluorobutylthio, 4-chlorobutylthio and 4-fluorobutylthio groups. The fluorine substituted groups are preferred. The fluoromethylthio, difluoromethylthio and trifluoromethylthio groups are most preferred, especially the trifluoromethylthio group.

Where R^1 represents an alkanoyl group, this has from 1 to 5 carbon atoms and may be a straight or branched chain group. Examples include the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl and pivaloyl groups, of which the formyl and acetyl groups are preferred.

Where R^1 represents a haloalkanoyl group, this has from 2 to 5 carbon atoms and may be a straight or branched chain group. Examples include the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, trichloroacetyl, bromoacetyl, iodoacetyl, 3-fluoropropionyl, 4-fluorobutyryl and 5-fluorovaleryl groups. Of

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these, the fluorine substituted alkanoyl groups are preferred, the fluoroacetyl, difluoroacetyl and trifluoroacetyl groups being more preferred and the trifluoroacetyl group being most preferred.

Where R^1 represents an alkoxycarbonyl group, this may be a straight or branched chain alkoxycarbonyl group having from 2 to 5 carbon atoms, that is the alkoxy part has from 1 to 4 carbon atoms, and examples include the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl and t-butoxycarbonyl groups. Of these, we prefer those alkoxycarbonyl groups having from 1 to 3 carbon atoms, more preferably the methoxycarbonyl and ethoxycarbonyl groups.

Where R^1 represents an alkanesulfonyl group, this may be a straight or branched chain alkanesulfonyl group having from 1 to 4 carbon atoms, and examples include the methanesulfonyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, isobutanesulfonyl, sec butanesulfonyl and t-butanesulfonyl groups. Of these, we prefer those alkanesulfonyl groups having from 1 to 3 carbon atoms, more preferably the methanesulfonyl and ethanesulfonyl groups.

Where R^1 represents a haloalkanesulfonyl group, the alkanesulfonyl part may be any one of the alkanesulfonyl groups exemplified above and may be substituted by one or more halogen (for example fluorine, chlorine, bromine or iodine) atoms. There is, in principle, no restriction on the number of halogen substituents on the alkanesulfonyl group, this being limited only by the number of substitutable atoms. In general, however, from 1 to 5 halogen substituents are preferred, from 1 to 3 substituents being more preferred. Specific examples of such groups include the fluoromethanesulfonyl, difluoromethanesulfonyl, trifluoromethanesulfonyl, dichloromethanesulfonyl, trichloromethanesulfonyl, 2-fluoroethanesulfonyl, 2-chloroethanesulfonyl, 2-bromoethanesulfonyl, 2-iodoethanesulfonyl, 2,2,2-trichloroethanesulfonyl, 2,2,2-trifluoroethanesulfonyl, 2-fluoropropanesulfonyl, 3-fluoropropanesulfonyl, 3-chloropropanesulfonyl, 2-fluorobutanesulfonyl, 3-fluorobutanesulfonyl, 4-chlorobutanesulfonyl and 4-fluorobutanesulfonyl groups. The fluorine-substituted alkanesulfonyl and chlorine substituted alkanesulfonyl groups are preferred, the fluorine-substituted alkanesulfonyl groups being more preferred. The fluoromethanesulfonyl, difluoromethanesulfonyl and trifluoromethanesulfonyl groups are most preferred, especially the trifluoromethanesulfonyl group.

Of the above groups and atoms, we especially prefer that R^1 should represent: a hydrogen atom; an alkyl group having from 1 to 4 carbon atoms; a halogen atom; a fluorine substituted alkyl group having from 1 to 4 carbon atoms; a hydroxy group; an alkoxy group having from 1 to 4 carbon atoms; a fluorine-substituted alkoxy group having from 1 to 4 carbon atoms; an alkylthio group having from 1 to 4 carbon atoms; a fluorine-substituted alkylthio group having from 1 to 4 carbon atoms; an amino group; an alkanoyl group having from 1 to 5 carbon atoms; a fluorine-substituted alkanoyl group having from 2 to 5 carbon atoms; an alkoxycarbonyl group having from 2 to 5 carbon atoms; a carbamoyl group; a cyano group; a nitro group; an alkanesulfonyl group having from 1 to 4 carbon atoms; a fluorine-substituted alkanesulfonyl group having from 1 to 4 carbon atoms; or a sulfamoyl group.

More preferably R^1 represents: a hydrogen atom; a methyl group; an ethyl group; a halogen atom; a fluo-

rine-substituted methyl group; a hydroxy group; a methoxy group; an ethoxy group; a fluorine-substituted methoxy group; a methylthio group; a fluorine-substituted methylthio group; a formyl group; an acetyl group; a fluorine-substituted acetyl group; a methoxycarbonyl group; an ethoxycarbonyl group; a propoxycarbonyl group; a carbamoyl group; a cyano group; a nitro group; a methanesulfonyl group; an ethanesulfonyl group; a fluorine-substituted methanesulfonyl group; or a sulfamoyl group.

Still more preferably R^1 represents: a halogen atom; a trifluoromethyl group; a hydroxy group; a difluoromethoxy group; a trifluoromethoxy group; a difluoromethylthio group; a trifluoromethylthio group; a formyl group; an acetyl group; a trifluoroacetyl group; a cyano group or a nitro group.

Most preferably R^1 represents: a fluorine atom, a chlorine atom or a trifluoromethyl group; especially a fluorine atom or a chlorine atom.

The number of the substituents, n , represented by R^1 is from 1 to 5, although the maximum may be lower than 5 in some cases if there is a problem of steric hindrance. Preferably n is from 1 to 3, and more preferably 1 or 2. The position of substitution by R^1 on the phenyl group is preferably para or ortho, more preferably ortho.

Where R^2 represents an alkanoyl group having from 1 to 10 carbon atoms, this may be a straight or branched chain group, and examples include the formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl and decanoyl groups, of which those groups having from 2 to 6 carbon atoms are preferred, especially the acetyl, propionyl and isobutyryl groups, of which the acetyl and propionyl groups are most preferred.

Those alkanoyl groups represented by R^2 and having from 2 to 10 carbon atoms may be substituted by one or more of substituents A, defined above. Examples of such substituents A include:

- halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms;
- hydroxy groups;
- alkoxy groups having from 1 to 4 carbon atoms, such as those exemplified above in relation to R^1 ; and
- cyano groups.

In the case of these substituted groups, and all substituted groups referred to herein, there is no specific limitation on the number of the substituents, except such as may be imposed by the number of substitutable positions and possibly also by steric constraints. However, in general, from 1 to 3 such substituents are preferred.

Specific examples of such substituted alkanoyl groups include the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, trichloroacetyl, bromoacetyl, iodoacetyl, 3-fluoropropionyl, 3-chloropropionyl, 3-bromopropionyl, 3-iodopropionyl, 4-fluorobutyryl, 4-chlorobutyryl, 5-fluorovaleryl, hydroxyacetyl, 3-hydroxypropionyl, 4-hydroxybutyryl, 5-hydroxyvaleryl, methoxyacetyl, 3-methoxypropionyl, 4-methoxybutyryl, 5-methoxyvaleryl, ethoxyacetyl, 3-ethoxypropionyl, 4-ethoxybutyryl, 5-ethoxyvaleryl, cyanoacetyl, 3-cyanopropionyl, 4-cyanobutyryl and 5-cyanovaleryl groups, of which the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, 3-fluoropropionyl, 3-chloropropionyl, hydroxyacetyl, 3-hydroxypropionyl, methoxyacetyl, 3-methoxypropionyl, ethoxyacetyl, cyanoacetyl and 3-cyanopropionyl groups are more preferred. Still more preferred are the fluoroacetyl, difluoroacetyl, trifluoro-

acetyl, chloroacetyl, 3-fluoropropionyl, hydroxyacetyl, methoxyacetyl, ethoxyacetyl and cyanoacetyl groups. The most preferred groups are the fluoroacetyl, difluoroacetyl, trifluoroacetyl, chloroacetyl, 3-fluoropropionyl, hydroxyacetyl, methoxyacetyl and cyanoacetyl groups, especially the fluoroacetyl, difluoroacetyl and trifluoroacetyl groups.

Where R^2 represents an alkenoyl group having from 3 to 6 carbon atoms, this may be a straight or branched chain group, and examples include the acryloyl, methacryloyl, 2-butenoyl, 2-pentenoyl and 2-hexenoyl groups, of which the acryloyl and methacryloyl groups are preferred.

These alkenoyl groups may also be substituted by one or more of substituents A, defined and exemplified above. Specific examples of such substituted groups include the 3-fluoroacryloyl, 3-chloroacryloyl and 3-cyanoacryloyl groups, of which the 3-fluoroacryloyl group is particularly preferred.

Where R^2 represents a cycloalkylcarbonyl group, this has from 4 to 8 carbon atoms, that is the cycloalkyl group itself has from 3 to 7 ring carbon atoms. Examples of such groups include the cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl and cycloheptylcarbonyl groups, of which the cyclopropylcarbonyl and cyclobutylcarbonyl groups are particularly preferred.

These cycloalkylcarbonyl groups may also be substituted by one or more of substituents A, defined and exemplified above. Specific examples of such substituted groups include the 2-fluorocyclopropylcarbonyl, 2,2-difluorocyclopropylcarbonyl, 2-chlorocyclopropylcarbonyl, 2-bromocyclopropylcarbonyl, 2-fluorocyclobutylcarbonyl, 2-chlorocyclobutylcarbonyl, 2-fluorocyclopentylcarbonyl, 2-chlorocyclopentylcarbonyl, 2-fluorocyclohexylcarbonyl, 2-chlorocyclohexylcarbonyl, 2-hydroxycyclopropylcarbonyl, 2-hydroxycyclobutylcarbonyl, 2-hydroxycyclopentylcarbonyl, 2-hydroxycyclohexylcarbonyl, 2-methoxycyclopropylcarbonyl, 2-methoxycyclobutylcarbonyl, 2-methoxycyclopentylcarbonyl, 2-methoxycyclohexylcarbonyl, 2-ethoxycyclopropylcarbonyl, 2-ethoxycyclobutylcarbonyl, 2-ethoxycyclopentylcarbonyl, 2-ethoxycyclohexylcarbonyl, 2-cyanocyclopropylcarbonyl, 2-cyanocyclobutylcarbonyl, 2-cyanocyclopentylcarbonyl and 2-cyanocyclohexylcarbonyl groups, of which the 2-fluorocyclopropylcarbonyl, 2,2-difluorocyclopropylcarbonyl, 2-chlorocyclopropylcarbonyl, 2-fluorocyclobutylcarbonyl, 2-chlorocyclobutylcarbonyl, 2-fluorocyclopentylcarbonyl, 2-fluorocyclohexylcarbonyl, 2-hydroxycyclopropylcarbonyl, 2-methoxycyclopropylcarbonyl, 2-ethoxycyclopropylcarbonyl and 2-cyanocyclopropylcarbonyl groups are preferred. More preferred groups are the 2-fluorocyclopropylcarbonyl, 2-chlorocyclopropylcarbonyl, 2-fluorocyclobutylcarbonyl and 2-methoxycyclopropylcarbonyl groups, and the most preferred is the 2-fluorocyclopropylcarbonyl group.

Where R^2 represents a substituted benzoyl group, this is substituted by at least one of substituents B, which are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms, all of which may be as exemplified in relation to the same groups and atoms represented by R^1 . The number of the substituents may be from 1 to 5, provided that there is no problem of steric hindrance; preferably, however, are from 1 to 3 substituents, more preferably 1 or Specific exam-

ples of such substituted benzoyl groups include the 2-fluorobenzoyl, 3-fluorobenzoyl, 4-fluorobenzoyl, 2,4-difluorobenzoyl, 2,4,6-trifluorobenzoyl, 2,3,4,5,6-pentafluorobenzoyl, 4-chlorobenzoyl, 2,4-dichlorobenzoyl, 4-methylbenzoyl, 2,4-dimethylbenzoyl, 4-ethylbenzoyl, 2,4-diethylbenzoyl, 4-methoxybenzoyl, 2,4-dimethoxybenzoyl, 4-ethoxybenzoyl and 2,4-diethoxybenzoyl groups, of which the 4-fluorobenzoyl and 2,4-difluorobenzoyl groups are preferred.

Where R^3 represents an alkoxy group, this may be a straight or branched chain group having from 1 to 4 carbon atoms and may be any of the alkoxy groups exemplified above in relation to R^1 . Such a group may be unsubstituted or it may have one or more substituents selected from the group consisting of substituents C, defined above, and examples of which are as follows:

alkoxy groups having from 1 to 4 carbon atoms, such as those exemplified above in relation to R^1 ;

alkanoyloxy groups having from 1 to 6 carbon atoms, which may be a straight or branched chain group, for example the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy or hexanoyloxy groups, of which those groups having from 1 to 5 carbon atoms are preferred, and the acetoxy, propionyloxy, butyryloxy and pivaloyloxy groups are most preferred; and

arylcabonyloxy groups in which the aryl part is as defined above, for example the arylcabonyloxy groups exemplified below in relation to R^3 .

Specific examples of such substituted alkoxy groups include the methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, formyloxymethoxy, acetoxymethoxy, propionyloxymethoxy, 2-formyloxyethoxy, 2-acetoxyethoxy, 2-propionyloxyethoxy, 3-acetoxypropoxy, 4-acetoxybutoxy, valeryloxymethoxy, pivaloyloxymethoxy, benzoyloxymethoxy, naphthoyloxymethoxy, p-toluoyloxymethoxy, p-chlorobenzoyloxymethoxy, 2-benzoyloxyethoxy, 3-benzoyloxypropoxy and 4-benzoyloxybutoxy groups, of which the pivaloyloxymethoxy group is most preferred.

Where R^3 represents an aralkyloxy group, the alkoxy part is an alkoxy group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1 , especially the methoxy, ethoxy, propoxy or isopropoxy groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1 . The alkoxy part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints; however, from 1 to 3 aryl groups are normally preferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyloxy groups include the benzyloxy, 1-naphthylmethoxy, 2-naphthylmethoxy, phenethyloxy, α -methylbenzyloxy, 3-phenylpropoxy, 2-phenylpropoxy, 1-phenylpropoxy, 4-phenylbutoxy, benzhydryloxy (i.e. diphenylmethoxy) and trityloxy (i.e. triphenylmethoxy) groups (of these, the benzyloxy and phenethyloxy groups are preferred), and such groups which are substituted by one or more of substituents D.

Where R^3 represents an alkanoyloxy group, this may be a straight or branched chain group and has from 1 to 18 carbon atoms. Examples of such groups include the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, pivaloyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, lauroyloxy, myristoyloxy, palmitoyloxy and stearoyloxy groups, of which those groups having from 1 to 12 carbon atoms are preferred, those having from 2 to 10 carbon atoms are more preferred, and those having from 2 to 5 carbon atoms are most preferred, especially the acetoxy, propionyloxy, butyryloxy, pivaloyloxy, nonanoyloxy and decanoyloxy groups, of which the acetoxy, propionyloxy, butyryloxy and pivaloyloxy groups are most preferred.

Where R^3 represents an alkenoyloxy group, this may be a straight or branched chain group and has from 3 to 6, more preferably 3 or 4, carbon atoms. Examples of such groups include the acryloyloxy, methacryloyloxy, 2-butenoyloxy, 2-pentenoyloxy and 2-hexenoyloxy groups, of which the acryloyloxy and methacryloyloxy groups are preferred.

Where R^3 represents a cycloalkylcarbonyloxy group, this has from 4 to 8, more preferably from 4 to 7, carbon atoms, that is the cycloalkyl group itself has from 3 to 7 ring carbon atoms. Examples of such groups include the cyclopropylcarbonyloxy, cyclobutylcarbonyloxy, cyclopentylcarbonyloxy, cyclohexylcarbonyloxy and cycloheptylcarbonyloxy groups, of which the cyclopropylcarbonyloxy and cyclobutylcarbonyloxy groups are particularly preferred.

Where R^3 represents an arylcarbonyloxy group, the aryl part is as defined above, and examples of such groups include the benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy, o-, m- and p-toluoyloxy, o-, m- and p-chlorobenzoyloxy, o-, m- and p-fluorobenzoyloxy, o-, m- and p-methoxybenzoyloxy, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dichlorobenzoyloxy, 2,4-difluorobenzoyloxy and 2,4,6-trifluorobenzoyloxy groups, preferably the benzoyloxy group.

Where R^3 represents an alkoxycarbonyloxy group, this may be a straight or branched chain alkoxycarbonyloxy group having from 2 to 5 carbon atoms, that is the alkoxy part has from 1 to 4 carbon atoms, and examples include the methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, isopropoxycarbonyloxy, butoxycarbonyloxy, isobutoxycarbonyloxy, sec-butoxycarbonyloxy and t-butoxycarbonyloxy groups. Of these, we prefer those alkoxycarbonyloxy groups having from 1 to 3 carbon atoms in the alkoxy part and the t-butoxycarbonyloxy group, more preferably the methoxycarbonyloxy, ethoxycarbonyloxy and t-butoxycarbonyloxy groups.

Where R^3 represents an aralkyloxycarbonyloxy group, the alkoxy part is an alkoxy group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1 , especially the methoxy, ethoxy, propoxy or isopropoxy groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1 . The alkoxy part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints;

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however, from 1 to 3 aryl groups are normally preferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyloxycarbonyloxy groups include the benzyloxycarbonyloxy, 1-naphthylmethoxycarbonyloxy, 2-naphthylmethoxycarbonyloxy, phenethyloxycarbonyloxy, α -methylbenzyloxy, carbonyloxy, 3-phenylpropoxycarbonyloxy, 2-phenylpropoxycarbonyloxy, 1-phenylpropoxycarbonyloxy, 4-phenylbutoxycarbonyloxy, benzhydryloxycarbonyloxy and trityloxycarbonyloxy groups (of these, the benzyloxycarbonyloxy group is preferred), and such groups which are substituted by one or more of substituents D.

Where R^3 represents a group of formula $-NR^aR^b$, R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one substituent selected from the group consisting of substituents C, defined above. Examples of the alkyl groups which may be represented by R^a and R^b are as given above in relation to R^1 , and examples of the substituted alkyl groups which may be represented by R^a and R^b are the substituted alkyl groups corresponding to the substituted alkoxy groups, as given above in relation to R^3 . Specific examples of these groups of formula $-NR^aR^b$ include amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, sec-butylamino, t-butylamino, dimethylamino, diethylamino, diisopropylamino, diisopropylamino, dibutylamino, methylethylamino, methylpropylamino, N-(methoxymethyl)amino, N-(2-methoxyethyl)amino, N-(acetoxymethyl)amino, N-(pivaloyloxymethyl)amino, N-(benzoylmethyl)amino, N-(2-acetoxyethyl)amino, N-(2-pivaloyloxymethyl)amino and N-(2-benzoyl)amino groups, preferably the amino, methylamino, ethylamino, N-(acetoxymethyl)amino and N-(pivaloyloxymethyl)amino groups.

Where R^3 represents an aralkylamino group, the alkyl part is an alkyl group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1 , especially the methyl, ethyl, propyl or isopropyl groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1 . The alkyl part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints; however, from 1 to 3 aryl groups are normally preferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyl amino groups include the benzylamino, N-(1-naphthylmethyl)amino, N-(2-naphthylmethyl)amino, phenethylamino, N-(α -methylbenzyl)amino, N-(3-phenylpropyl)amino, N-(2-phenylpropyl)amino, N-(1-phenylpropyl)amino, N-(4-phenylbutyl)amino, benzhydrylamino and tritylamino groups (of these, the benzylamino group is preferred), and such groups which are substituted by one or more of substituents D.

Where R^3 represents an alkanoylamino group, this may be a straight or branched chain group and has from 1 to 18 carbon atoms. Examples of such groups include

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the formamido, acetamido, propionamido, butyramido, isobutyramido, valerylamino, isovalerylamino, pivaloylamino, hexanoylamino, heptanoylamino, octanoylamino, nonanoylamino, decanoylamino, lauroylamino, myristoylamino, palmitoylamino and stearoylamino groups, of which those groups having from 1 to 12 carbon atoms are preferred, those having from 2 to 10 carbon atoms are more preferred, and those having from 2 to 5 carbon atoms are most preferred, especially the acetamido, propionamido, butyramido, pivaloylamino, nonanoylamino and decanoylamino groups, of which the acetamido, propionamido, butyramido and pivaloylamino groups are most preferred.

Where R^3 represents an alkenoylamino group, this may be a straight or branched chain group and has from 3 to 6 carbon atoms. Examples of such groups include the acryloylamino, methacryloylamino, 2-butenoylamino, 2-pentenoylamino and 2-hexenoylamino groups, of which the acryloylamino and methacryloylamino groups are preferred.

Where R^3 represents a cycloalkylcarbonylamino group, this has from 4 to 8 carbon atoms, that is the cycloalkyl group itself has from 3 to 7 ring carbon atoms. Examples of such groups include the cyclopropylcarbonylamino, cyclobutylcarbonylamino, cyclopentylcarbonylamino, cyclohexylcarbonylamino and cycloheptylcarbonylamino groups, of which the cyclopropylcarbonylamino and cyclobutylcarbonylamino groups are particularly preferred.

Where R^3 represents arylcarbonylamino group, the aryl part is as defined above, and examples of such groups include the benzamido, 1-naphthoylamino, 2-naphthoylamino, o-, m- and p-toluoylamino, o-, m- and p-chlorobenzamido, o-, m- and p-fluorobenzamido, o-, m- and p-methoxybenzamido, 2,4-dichlorobenzamido, 2,4-difluorobenzamido and 2,4,6-trifluorobenzamido groups, preferably the benzamido group.

Where R^3 represents an alkoxycarbonylamino group, this may be a straight or branched chain alkoxycarbonylamino group having from 2 to 5 carbon atoms, that is the alkoxy part has from 1 to 4 carbon atoms, add examples include the methoxycarbonylamino, ethoxycarbonylamino, propoxycarbonylamino, isopropoxycarbonylamino, butoxycarbonylamino, isobutoxycarbonylamino, sec-butoxycarbonylamino and t-butoxycarbonylamino groups. Of these, we prefer those alkoxycarbonylamino groups having from 1 to 3 carbon atoms in the alkoxy part and the t-butoxycarbonylamino group, more preferably the methoxycarbonylamino, ethoxycarbonylamino and t-butoxycarbonylamino groups.

Where R^3 represents an aralkoxycarbonylamino group, the alkoxy part is an alkoxy group having from 1 to 4, preferably from 1 to 3, carbon atoms, such as those exemplified above in relation to R^1 , especially the methoxy, ethoxy, propoxy or isopropoxy groups. The aryl part is as defined above and has from 6 to 10, preferably 6 or 10, ring carbon atoms. Examples of such aryl groups include the phenyl, 1-naphthyl and 2-naphthyl groups and such groups which are substituted by one or more of substituents D, defined above and examples of which have been given in relation to the same groups and atoms which may be represented by R^1 . The alkoxy part may be substituted by one or more aryl groups, the maximum being dictated only by the number of substitutable positions and possibly also by steric constraints; however, from 1 to 3 aryl groups are normally pre-

ferred, 1 or 2 being more preferred and 1 being most preferred. Specific examples of the aralkyloxycarbonylamino groups include the benzyloxycarbonylamino, N-(1-naphthylmethoxycarbonyl)amino, N-(2-naphthylmethoxycarbonyl)amino, phenethyloxycarbonylamino, N-(α -methylbenzyloxycarbonyl)amino, N-(3-phenylpropoxycarbonyl)amino, N-(2-phenylpropoxycarbonyl)amino, N-(1-phenylpropoxycarbonyl)amino, N-(4-phenylbutoxycarbonyl)amino, benzhydryloxycarbonylamino and trityloxycarbonylamino groups (of these, the benzyloxycarbonylamino group is preferred), and such groups which are substituted by one or more of substituents D.

Y represents a group of formula —NH— or an oxygen or sulfur atom, preferably an oxygen or sulfur atom, and more preferably a sulfur atom.

R³ may be at either the 2- or the 3- position of the tetrahydropyrrolopyridyl, tetrahydrothienopyridyl or tetrahydrofuropyridyl group, but is preferably at the 2-position, especially when the Y is an oxygen or sulfur atom, i.e. on the tetrahydrothienopyridyl or tetrahydrofuropyridyl group.

In the compounds of the present invention, the carbon atom to which the group represented by R² is attached is an assymmetric carbon atom, and other carbon atoms may be assymmetric, and the compounds accordingly form optical isomers. Although these are all represented herein by a single molecular formula, the present invention includes both the individual, isolated isomers and mixtures, including racemates thereof. Where stereospecific synthesis techniques are employed or optically active compounds are employed as starting materials, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques.

In addition, when the compounds of the present invention have one or more carbon-carbon double bonds or one or more disubstituted cycloalkyl moieties, they form cis and trans isomers. The present invention includes both the individual, isolated isomers and mixtures thereof.

The compounds of the present invention can form acid addition salts. There is no particular restriction on the nature of these salts, provided that, where they are intended for therapeutic use, they are pharmaceutically acceptable. Where they are intended for non-therapeutic uses, e.g. as intermediates in the preparation of other, and possibly more active, compounds, even this restriction does not apply. Examples of such acid addition salts include: salts with mineral acids, especially hydrohalic acids (such as hydrofluoric acid, hydrobromic acid, hydroiodic acid or hydrochloric acid), nitric acid, carbonic acid, sulfuric acid or phosphoric acid; salts with lower alkylsulfonic acids, such as methanesulfonic acid, trifluoromethanesulfonic acid or ethanesulfonic acid; salts with arylsulfonic acids, such as benzenesulfonic acid or p-toluenesulfonic acid; and salts with organic carboxylic acids, such as acetic acid, propionic acid, butyric acid, fumaric acid, tartaric acid, oxalic acid, malonic acid, maleic acid, malic acid, succinic acid, benzoic acid, mandelic acid, ascorbic acid, lactic acid, gluconic acid or citric acid.

The compounds of the present invention may also readily form hydrates and these, also, form part of the present invention.

Additionally, when R³ represents an amino group or a substituted amino group, the resulting compound can

form a complex salt with a metal ion, and such complex salts also form part of the present invention. Examples of such complex salts include salts with calcium chloride, magnesium chloride, zinc chloride, ferric chloride, stannic chloride and nickel chloride.

Preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(A) R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group.

(B) R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a substituted benzoyl group having at least one fluorine substituent, or a 5,6-dihydro-1,4,2-dioxazin-3-yl group; and

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups.

(C) R³ represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $\text{—NR}^a\text{R}^b$

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wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5

carbon atoms, a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D' , defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D' , defined below;

and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

(D) Y represents an oxygen or sulfur atom.

Of these, we prefer those compounds in which R^1 is as defined in (A) above, R^2 is as defined in (B) above, R^3 is as defined in (C) above and Y is as defined in (D) above.

More preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(E) R^1 represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group.

(F) R^2 represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom.

(G) R^3 represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyl group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

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Of these, we prefer those compounds in which R^1 is as defined in (E) above, R^2 is as defined in (F) above, R^3 is as defined in (G) above and Y is as defined in (D) above.

Still more preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(H) R^1 represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group.

(I) R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

(J) Y represents a sulfur atom.

Of these, we prefer those compounds in which R^1 is as defined in (H) above, R^2 is as defined in (F) above, R^3 is as defined in (I) above and Y is as defined in (J) above.

The most preferred classes of compounds of the present invention are those compounds of formulae (I) and tautomers and salts thereof in which:

(K) R^1 represents a fluorine or chlorine atom.

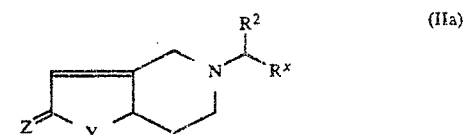
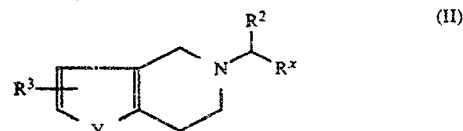
(L) R^2 represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom.

(M) R^3 represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

Of these, we prefer those compounds in which R^1 is as defined in (K) above, R^2 is as defined in (L) above, R^3 is as defined in (M) above and Y is as defined in (J) above.

In all of the above classes of compounds, we prefer that n should be from 1 to 3, especially 1 or 2, and most preferably 1.

Specific examples of preferred compounds of the present invention are those compounds of formula (II) or (IIa), in which R^x , R^2 , R^3/Z and Y are as defined in the following Table 1. In the column headed " R^3/Z ", the " R^3 " applies to compounds of formula (II), whilst " Z " applies to compounds of formula (IIa):



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In the Table, the following abbreviations are used to refer to certain substituent groups:

Ac	acetyl
Acr	acryloyl
tBoc	t-butoxycarbonyl
Boz	benzoyl
cBu	cyclobutyl
tBu	t-butyl
Bun	butenoyl
Byr	butyryl
iByr	isobutyryl
Bz	benzyl
Bzc	benzyloxycarbonyl
Car	carbamoyl
Dcn	decanoyl
Ddoz	5,6-dihydro-1,4,2-dioxazin-3-yl
Et	ethyl
Etc	ethoxycarbonyl
Fo	formyl
cHp	cycloheptyl
cHx	cyclohexyl
Hxn	hexanoyl
Lau	lauroyl
Me	methyl
Mec	methoxycarbonyl
Mod	(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl
Nnn	nonanoyl
Pit	palmitoyl
Ph	phenyl
Phth	phthalidyl
Piv	pivaloyl
cPn	cyclopentyl
cPr	cyclopropyl
Prn	propionyl
Va	valeryl
iVa	isovaleryl

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TABLE 1-continued

Cpd. No.	For- mula	R ¹	R ²	R ³ /Z	Y
5	(II)	2-MeSO ₂ Ph	Prn	H	S
	(II)	2-EtSO ₂ Ph	Prn	H	S
	(II)	2-CF ₃ SO ₂ Ph	Prn	H	S
	(II)	4-CarPh	Prn	H	S
	(II)	3-NH ₂ SO ₂ Ph	Prn	H	S
10	(II)	2-FoPh	Prn	H	S
	(II)	2-AcPh	Prn	H	S
	(II)	2-CF ₃ COPh	Prn	H	S
	(II)	2,6-diFPh	Prn	H	S
	(II)	2-F, 6-ClPh	Prn	H	S
15	(II)	2,4,6-triFPh	Prn	H	S
	(II)	2,3,4,5,6-pentaFPh	Prn	H	S
	(II)	2-F, 6-CNPh	Prn	H	S
	(II)	2-F, 6-NO ₂ Ph	Prn	H	S
	(II)	2,6-diF, 4-MePh	Prn	H	S
20	(II)	2,4-diClPh	Prn	H	S
	(II)	2-F, 4-HOPh	Prn	H	S
	(II)	2-Cl, 4-MecPh	Prn	H	S
	(II)	2-F, 6-CHF ₂ OPh	Prn	H	S
	(II)	2-Cl, 4-EtPh	Prn	H	S
25	(II)	2-F, 5-EtOPh	Prn	H	S
	(II)	Ph	cPrCO	H	S
	(II)	2-FPh	cPrCO	H	S
	(II)	2-ClPh	cPrCO	H	S
	(II)	2-BrPh	cPrCO	H	S
30	(II)	2-IPh	cPrCO	H	S
	(II)	2-HOPh	cPrCO	H	S
	(II)	2-NO ₂ Ph	cPrCO	H	S
	(II)	2-Cl, 5-NH ₂ Ph	cPrCO	H	S
	(II)	2-CNPh	cPrCO	H	S
35	(II)	2-F, 5-HOOCPh	cPrCO	H	S
	(II)	2-F, 4-MePh	cPrCO	H	S
	(II)	2-CF ₃ Ph	cPrCO	H	S
	(II)	2-F, 4-MeOPh	cPrCO	H	S
	(II)	2-CHF ₂ OPh	cPrCO	H	S
40	(II)	2-CF ₃ OPh	cPrCO	H	S
	(II)	3-CH ₂ FOPh	cPrCO	H	S
	(II)	4-MeSPh	cPrCO	H	S
	(II)	2-CHF ₂ SPh	cPrCO	H	S
	(II)	3-CF ₃ SPh	cPrCO	H	S
45	(II)	2-MeSO ₂ Ph	cPrCO	H	S
	(II)	2-EtSO ₂ Ph	cPrCO	H	S
	(II)	2-CF ₃ SO ₂ Ph	cPrCO	H	S
	(II)	4-CarPh	cPrCO	H	S
	(II)	3-NH ₂ SO ₂ Ph	cPrCO	H	S
50	(II)	2-FoPh	cPrCO	H	S
	(II)	2-AcPh	cPrCO	H	S
	(II)	2-CF ₃ COPh	cPrCO	H	S
	(II)	2,6-diFPh	cPrCO	H	S
	(II)	2-F, 6-ClPh	cPrCO	H	S
55	(II)	2,4,6-triFPh	cPrCO	H	S
	(II)	2,3,4,5,6-pentaFPh	cPrCO	H	S
	(II)	2-F, 6-CNPh	cPrCO	H	S
	(II)	2-F, 6-NO ₂ Ph	cPrCO	H	S
	(II)	2,6-diF, 4-MePh	cPrCO	H	S
60	(II)	2,4-diClPh	cPrCO	H	S
	(II)	2-F, 4-HOPh	cPrCO	H	S
	(II)	2-Cl, 4-EtPh	cPrCO	H	S
	(II)	2-F, 6-CHF ₂ OPh	cPrCO	H	S
	(II)	2-Cl, 4-EtPh	cPrCO	H	S
65	(II)	2-F, 5-EtOPh	cPrCO	H	S
	(II)	2-FPh	3-FPrn	H	S
	(II)	2-ClPh	3-FPrn	H	S
	(II)	2-CNPh	3-FPrn	H	S
	(II)	2,6-diFPh	3-FPrn	H	S
70	(II)	2-F, 6-ClPh	3-FPrn	H	S
	(II)	2,4,6-triFPh	3-FPrn	H	S
	(II)	2,3,4,5,6-pentaFPh	3-FPrn	H	S
	(II)	2-F, 6-CNPh	3-FPrn	H	S
	(II)	2-F, 6-NO ₂ Ph	3-FPrn	H	S
75	(II)	2,6-diF, 4-MePh	3-FPrn	H	S
	(II)	2,4-diClPh	3-FPrn	H	S
	(II)	2-F, 4-HOPh	3-FPrn	H	S
	(II)	2-Cl, 4-EtPh	3-FPrn	H	S
	(II)	2-F, 6-CHF ₂ OPh	3-FPrn	H	S
80	(II)	2-Cl, 4-EtPh	3-FPrn	H	S
	(II)	2-F, 5-EtOPh	3-FPrn	H	S
	(II)	2-FPh	3-FPrn	H	S
	(II)	2-ClPh	3-FPrn	H	S
	(II)	2-CNPh	3-FPrn	H	S
85	(II)	2,6-diFPh	3-FPrn	H	S
	(II)	2-F, 6-ClPh	3-FPrn	H	S
	(II)	2,4,6-triFPh	3-FPrn	H	S
	(II)	2,3,4,5,6-pentaFPh	3-FPrn	H	S
	(II)	2-F, 6-CNPh	3-FPrn	H	S
90	(II)	2-F, 6-NO ₂ Ph	3-FPrn	H	S
	(II)	2,6-diF, 4-MePh	3-FPrn	H	S
	(II)	2,4-diClPh	3-FPrn	H	S
	(II)	2-F, 4-HOPh	3-FPrn	H	S
	(II)	2-Cl, 4-EtPh	3-FPrn	H	S
95	(II)	2-F, 6-CHF ₂ OPh	3-FPrn	H	S
	(II)	2-Cl, 4-EtPh	3-FPrn	H	S
	(II)	2-F, 5-EtOPh	3-FPrn	H	S
	(II)	2-FPh	3-FPrn	H	S
	(II)	2-ClPh	3-FPrn	H	S
100	(II)	2-CNPh	3-FPrn	H	S
	(II)	2,6-diFPh	3-FPrn	H	S
	(II)	2-F, 6-ClPh	3-FPrn	H	S
	(II)	2-F, 6-CNPh	3-FPrn	H	S
	(II)	2-NO ₂ Ph	3-FPrn	H	S
105	(II)	2-F, 4-CNPh	3-FPrn	H	S
	(II)	2-FPh	cBuCO	H	S
	(II)	2-F, 6-CHF ₂ OPh	cBuCO	H	S
	(II)	2-Cl, 4-EtPh	cBuCO	H	S
	(II)	2-F, 5-EtOPh	cBuCO	H	S

TABLE 1

Cpd. No.	For- mula	R ¹	R ²	R ³ /Z	Y
1	(II)	Ph	Ddoz	H	S
2	(II)	2-FPh	Ddoz	H	S
3	(II)	2-ClPh	Ddoz	H	S
4	(II)	2-CNPh	Ddoz	H	S
5	(II)	2-NO ₂ Ph	Ddoz	H	S
6	(II)	2-CHF ₂ Ph	Ddoz	H	S
7	(II)	2,6-diFPh	Ddoz	H	S
8	(II)	2-F, 6-ClPh	Ddoz	H	S
9	(II)	2-FPh	Ac	H	S
10	(II)	2-ClPh	Ac	H	S
11	(II)	2-CNPh	Ac	H	S
12	(II)	2-NO ₂ Ph	Ac	H	S
13	(II)	2-CF ₃ Ph	Ac	H	S
14	(II)	2,6-diFPh	Ac	H	S
15	(II)	2-F, 6-ClPh	Ac	H	S
16	(II)	2,4-diFPh	Ac	H	S
17	(II)	2-F, 6-CNPh	Ac	H	S
18	(II)	Ph	Prn	H	S
19	(II)	2-FPh	Prn	H	S
20	(II)	2-ClPh	Prn	H	S
21	(II)	2-BrPh	Prn	H	S
22	(II)	2-IPh	Prn	H	S
23	(II)	2-HOPh	Prn	H	S
24	(II)	2-NO ₂ Ph	Prn	H	S
25	(II)	2-Cl, 5-NH ₂ Ph	Prn	H	S
26	(II)	2-CNPh	Prn	H	S
27	(II)	2-F, 5-HOOCPh	Prn	H	S
28	(II)	2-F, 4-MePh	Prn	H	S
29	(II)	2-CF ₃ Ph	Prn	H	S
30	(II)	2-F, 4-MeOPh	Prn	H	S
31	(II)	2-CHF ₂ OPh	Prn	H	S
32	(II)	2-CF ₃ OPh	Prn	H	S
33	(II)	3-CH ₂ FOPh	Prn	H	S
34	(II)	4-MeSPh	Prn	H	S
35	(II)	2-CHF ₂ SPh	Prn	H	S
36	(II)	3-CF ₃ SPh	Prn	H	S

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TABLE 1-continued

Cpd. No.	Formula	R ¹	R ²	R ³ /Z	Y
107	(II)	2-ClPh	cBuCO	H	S
108	(II)	2-CNPh	cBuCO	H	S
109	(II)	2-FPh	HOCH ₂ CO	H	S
110	(II)	2-ClPh	HOCH ₂ CO	H	S
111	(II)	2-CNPh	CF ₃ CO	H	S
112	(II)	2-FPh	CF ₃ CO	H	S
113	(II)	2-ClPh	CF ₃ CO	H	S
114	(II)	2-FPh	Fo	H	S
115	(II)	2-ClPh	Fo	H	S
116	(II)	2-FPh	Byr	H	S
117	(II)	2-ClPh	Byr	H	S
118	(II)	2-FPh	iByr	H	S
119	(II)	2-ClPh	iByr	H	S
120	(II)	2-FPh	Va	H	S
121	(II)	2-ClPh	Va	H	S
122	(II)	2-FPh	Piv	H	S
123	(II)	2-F, 6-ClPh	Piv	H	S
124	(II)	2-FPh	iVa	H	S
125	(II)	2-ClPh	Hxn	H	S
126	(II)	2-FPh	Dcn	H	S
127	(II)	2-ClPh	1-Bun	H	S
128	(II)	2-FPh	cPnCO	H	S
129	(II)	2-FPh	cHxCO	H	S
130	(II)	2-FPh	cHpCO	H	S
131	(II)	2-FPh	CH ₂ FCO	H	S
132	(II)	2-FPh	CHF ₂ CO	H	S
133	(II)	2-ClPh	CHF ₂ CO	H	S
134	(II)	2-CNPh	CHF ₂ CO	H	S
135	(II)	2-FPh	MeO—CH ₂ CO	H	S
136	(II)	2-ClPh	MeO—CH ₂ CO	H	S
137	(II)	2-FPh	NC—CH ₂ CO	H	S
138	(II)	2-ClPh	NC—CH ₂ CO	H	S
139	(II)	2,6-diFPh	NC—CH ₂ CO	H	S
140	(II)	2-FPh	3-ClPrn	H	S
141	(II)	2-ClPh	3-ClPrn	H	S
142	(II)	2-FPh	3-HOPrn	H	S
143	(II)	2-ClPh	3-HOPrn	H	S
144	(II)	2-FPh	3-MeOPrn	H	S
145	(II)	2-FPh	3-CNPrn	H	S
146	(II)	2-FPh	4-FByr	H	S
147	(II)	2-ClPh	4-ClByr	H	S
148	(II)	2-FPh	4-FBoz	H	S
149	(II)	2-ClPh	4-FBoz	H	S
150	(II)	2-CNPh	4-FBoz	H	S
151	(II)	2-FPh	2,4-diFBoz	H	S
152	(II)	2-ClPh	2,4-diFBoz	H	S
153	(II)	2-NO ₂ Ph	2,4-diFBoz	H	S
154	(II)	2-FPh	3-BrPrn	H	S
155	(II)	2-FPh	3-IPrn	H	S
156	(II)	2-FPh	Ac	H	O
157	(II)	2-ClPh	Ac	H	O
158	(II)	2-CNPh	Ac	H	O
159	(II)	2-NO ₂ Ph	Ac	H	O
160	(II)	2-FPh	Prn	H	O
161	(II)	2-ClPh	Prn	H	O
162	(II)	2-CNPh	Prn	H	O
163	(II)	2-NO ₂ Ph	Prn	H	O
164	(II)	2-FPh	3-FPrn	H	O
165	(II)	2-ClPh	3-FPrn	H	O
166	(II)	2-CNPh	3-FPrn	H	O
167	(II)	2-NO ₂ Ph	3-FPrn	H	O
168	(II)	2-FPh	cPrCO	H	O
169	(II)	2-ClPh	cPrCO	H	O
170	(II)	2-CNPh	cPrCO	H	O
171	(II)	2-NO ₂ Ph	cPrCO	H	O
172	(II)	2,6-diFPh	cPrCO	H	O
173	(II)	2-F, 6-ClPh	cPrCO	H	O
174	(II)	2,6-diFPh	4-FBoz	H	S
175	(II)	2-FPh	cPrCO	2-NO ₂	S
176	(II)	2-FPh	cPrCO	2-NH ₂	O
177	(II)	2-FPh	cPrCO	2-NH ₂	S
178	(II)	2-FPh	cPrCO	2-AcNH	O
179	(II)	2-FPh	cPrCO	2-AcNH	S
180	(II)	2-FPh	cPrCO	2-ByrNH	O
181	(II)	2-FPh	cPrCO	2-ByrNH	S
182	(II)	2-FPh	cPrCO	2-PivNH	S
183	(II)	2-FPh	cPrCO	2-tBocNH	O
184	(II)	2-FPh	cPrCO	2-tBocNH	S
185	(II)	2-FPh	cPrCO	2-HO	O
186	(II)	2-ClPh	cPrCO	2-HO	S

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TABLE 1-continued

Cpd. No.	Formula	R ¹	R ²	R ³ /Z	Y
187	(II)	2-FPh	Prn	2-HO	S
188	(II)	2-FPh	cPrCO	2-HO	S
189	(II)	2-FPh	cPrCO	2-AcO	O
190	(II)	2-FPh	cPrCO	2-AcO	S
191	(II)	2-FPh	cPrCO	2-PrnO	O
192	(II)	2-FPh	cPrCO	2-PrnO	S
193	(II)	2-FPh	cPrCO	2-ByrO	O
194	(II)	2-FPh	cPrCO	2-ByrO	S
195	(II)	2-FPh	cPrCO	2-PivO	O
196	(II)	2-FPh	cPrCO	2-PivO	S
197	(II)	2-FPh	cPrCO	2-VaO	S
198	(II)	2-FPh	cPrCO	2-HxnO	S
199	(II)	2-FPh	cPrCO	2-NnnO	S
200	(II)	2-FPh	cPrCO	2-DcnO	S
201	(II)	2-FPh	cPrCO	2-PltO	S
202	(II)	2-FPh	cPrCO	2-BozO	S
203	(II)	2-FPh	cPrCO	2-tBocO	S
204	(II)	2-FPh	cPrCO	2-iBuO	S
205	(II)	2-FPh	cPrCO	2-BzO	S
206	(II)	2-FPh	cPrCO	2-MeOCH ₂ O	S
207	(II)	2-FPh	cPrCO	2-PivOCH ₂ O	S
208	(II)	2-FPh	cPrCO	2-PhthO	S
209	(II)	2-FPh	cPrCO	2-ModO	S
210	(II)	2-FPh	cPrCO	2-MeO	S
211	(II)	2-FPh	cPrCO	2-EtO	S
212	(II)	2-FPh	cPrCO	2-LauO	S
213	(II)	2-FPh	cPrCO	2-AcrO	S
214	(II)	2-FPh	cPrCO	2-cHxCOO	S
215	(II)	2-FPh	cPrCO	2-MecO	S
216	(II)	2-FPh	cPrCO	2-EtcO	S
217	(II)	2-FPh	cPrCO	2-FoNH	S
218	(II)	2-FPh	cPrCO	2-PrnNH	S
219	(II)	2-FPh	cPrCO	2-MeNH	S
220	(II)	2-FPh	cPrCO	2-EtNH	S
221	(II)	2-FPh	cPrCO	2-NMe ₂	S
222	(II)	2-FPh	cPrCO	2-AcrNH	S
223	(II)	2-FPh	cPrCO	2-cHxCONH	S
224	(II)	2-FPh	cPrCO	2-MecNH	S
225	(II)	2-FPh	cPrCO	2-EtcNH	S
226	(II)	2-FPh	cPrCO	2-BozNH	S
227	(II)	2-FPh	cPrCO	2-BozO	O
228	(II)	2-FPh	cPrCO	2-tBocO	O
229	(II)	2-FPh	Prn	2-NO ₂	S
230	(II)	2-FPh	cPrCO	2-BzO	S
231	(II)	2-FPh	cPrCO	2-BzcNH	S
232	(IIa)	2-FPh	cPrCO	O	O
233	(IIa)	2-ClPh	cPrCO	O	S
234	(IIa)	2-FPh	Prn	O	S
235	(IIa)	2-FPh	cPrCO	O	S
236	(II)	2-FPh	Prn	2-AcO	S
237	(II)	2-FPh	Prn	2-PrnO	S
238	(II)	2-FPh	Prn	2-ByrO	S
239	(II)	2-FPh	Prn	2-PivO	S
240	(II)	2-FPh	Prn	2-VaO	S
241	(II)	2-FPh	Prn	2-HxnO	S
242	(II)	2-FPh	Prn	2-MecO	S
243	(II)	2-FPh	Prn	2-EtcO	S
244	(II)	2-FPh	Prn	2-tBocO	S
245	(II)	2-FPh	Prn	2-BozO	S
246	(II)	2-FPh	Prn	2-NH ₂	S
247	(II)	2-FPh	Prn	2-AcNH	S
248	(II)	2-FPh	Prn	2-PrnNH	S
249	(II)	2-FPh	Prn	2-ByrNH	S
250	(II)	2-FPh	Prn	2-tBocNH	S
251	(II)	2-FPh	Prn	2-BzcNH	S
252	(II)	2-ClPh	cPrCO	2-AcO	S
253	(II)	2-ClPh	cPrCO	2-PrnO	S
254	(II)	2-ClPh	cPrCO	2-ByrO	S
255	(II)	2-ClPh	cPrCO	2-PivO	S
256	(II)	2-ClPh	cPrCO	2-VaO	S
257	(II)	2-ClPh	cPrCO	2-HxnO	S
258	(II)	2-ClPh	cPrCO	2-MecO	S
259	(II)	2-ClPh	cPrCO	2-EtcO	S
260	(II)	2-ClPh	cPrCO	2-tBocO	S
261	(II)	2-ClPh	cPrCO	2-BozO	S
262	(II)	2-ClPh	cPrCO	2-NH ₂	S
263	(II)	2-ClPh	cPrCO	2-AcNH	S
264	(II)	2-ClPh	cPrCO	2-PrnNH	S
265	(II)	2-ClPh	cPrCO	2-ByrNH	S
266	(II)	2-ClPh	cPrCO	2-tBocNH	S

TABLE 1-continued

Cpd. No.	Formula	R ^x	R ²	R ³ /Z	Y
267	(II)	2-ClPh	cPrCO	2-BzNH	S
268	(II)	2-FPh	cPrCO	2-MeOCH ₂ NH	S
269	(II)	2-FPh	cPrCO	2-PhthNH	S
270	(II)	2-FPh	cPrCO	2-ModNH	S
271	(II)	2-FPh	cPrCO	2-PivOCH ₂ NH	S
272	(II)	2-FPh	2-FcPrCO	H	S
273	(II)	2-FPh	2-FcPrCO	H	O
274	(II)	2-FPh	2-FcPrCO	2-OH	S
275	(IIa)	2-FPh	2-FcPrCO	O	S
276	(II)	2-FPh	2-FcPrCO	2-AcO	S
277	(II)	2-FPh	2-FcPrCO	2-ByrO	S
278	(II)	2-FPh	2-FcPrCO	2-PivO	S
279	(II)	2-FPh	2-FcPrCO	2-PivOCH ₂ O	S
280	(II)	2-ClPh	2-FcPrCO	H	S
281	(II)	2-ClPh	2-FcPrCO	2-OH	S
282	(IIa)	2-ClPh	2-FcPrCO	O	S
283	(II)	2-ClPh	2-FcPrCO	2-AcO	S
284	(II)	2-ClPh	2-FcPrCO	2-ByrO	S
285	(II)	2-ClPh	2-FcPrCO	2-PivO	S
286	(II)	2-ClPh	2-FcPrCO	2-PivOCH ₂ O	S
287	(II)	2-FPh	2,2-diFcPrCO	H	S
288	(II)	2-FPh	2,2-diFcPrCO	2-OH	S
289	(IIa)	2-FPh	2,2-diFcPrCO	O	S
290	(II)	2-FPh	2,2-diFcPrCO	2-AcO	S
291	(II)	2-FPh	2,2-diFcPrCO	2-ByrO	S

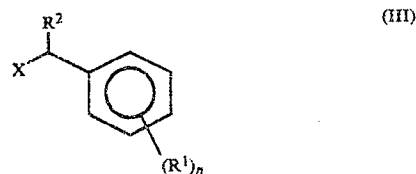
Of the compounds listed above, the following are preferred, that is to say Compounds No. 2, 3, 7, 9, 10, 11, 12, 19, 20, 24, 26, 29, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 89, 90, 98, 99, 106, 107, 108, 109, 111, 112, 113, 114, 116, 117, 118, 119, 120, 121, 122, 124, 125, 128, 129, 131, 132, 133, 135, 137, 140, 142, 144, 149, 151, 156, 160, 168, 177, 184, 186, 187, 188, 190, 192, 194, 196, 197, 198, 199, 200, 201, 203, 204, 206, 207, 208, 209, 210, 233, 234, 235, 236, 238, 239, 252, 253, 254, 255, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289 and 290, of which Compounds No. 9, 10, 19, 20, 59, 60, 63, 64, 66, 69, 71, 72, 75, 76, 83, 84, 85, 86, 98, 106, 113, 116, 118, 120, 122, 125, 128, 129, 131, 132, 186, 187, 188, 190, 192, 194, 196, 197, 198, 199, 200, 203, 207, 209, 233, 234, 235, 236, 238, 239, 252, 253, 254, 255, 274, 275, 276, 277, 278, 279, 281, 282, 283, 284, 285 and 286 are more preferred.

The most preferred compounds are Compounds No.:

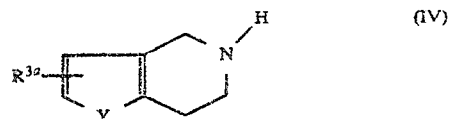
19. 5-(2-Fluoro- α -propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
59. 5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
60. 5-(2-Chloro-60 -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
190. 2-Acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
192. 5-(-60 Cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
194. 2-Butyryloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
196. 5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
197. 5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

198. 5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
203. 2-t-Butoxycarbonyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
207. 5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
233. 5-(2-Chloro- α -cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
234. 5-(2-Fluoro- α -propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
235. 5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
252. 2-Acetoxy-5-(2-chloro- α -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
275. 5[α -(2-Fluorocyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;
276. 2-Acetoxy-5-[α -(2-fluorocyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

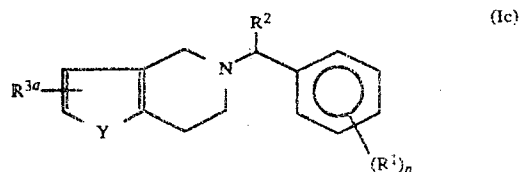
The compounds of the present invention can be prepared by a variety of methods, whose general techniques are known in the art for the preparation of compounds of this type. For example, they may be prepared by reacting a compound of formula (III):



(in which R¹, R² and n are as defined above and X represents a halogen atom, for example a fluorine, chlorine, bromine or iodine atom, preferably a chlorine or bromine atom) with a compound of formula (IV):



(in which Y is as defined above and R^{3a} represents a hydrogen atom or a hydroxy or nitro group) to give a compound of formula (Ic):



(in which R¹, R², R^{3a}, n and Y are as defined above). If required, this compound of formula (Ic) may then be subjected to one or more appropriate reactions, as explained in more detail hereafter, to convert the hy-

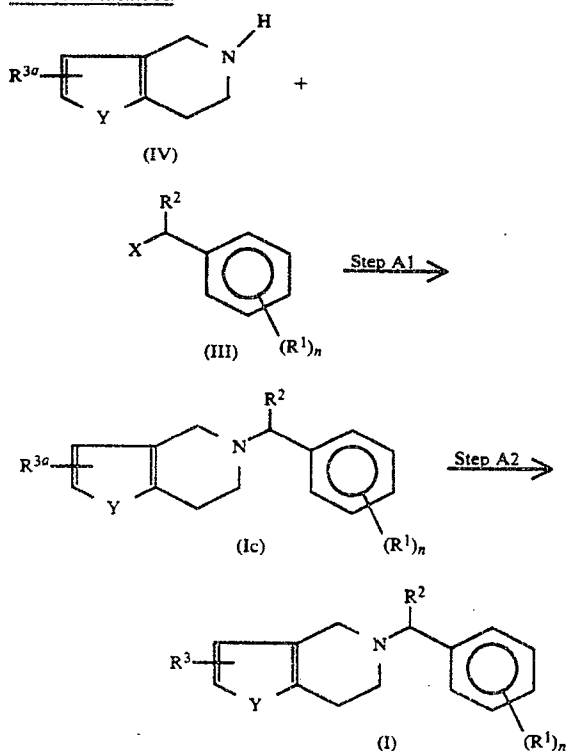
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droxy or nitro group represented by R^{3a} to any other group represented by R^3 , as defined above.

These reactions may be summarized in the following Reaction Scheme A:

Reaction Scheme A:



In the above formulae, R^1 , R^2 , R^3 , R^{3a} , X , Y and n are as defined above.

In Step A1 of this Reaction Scheme, the substituted benzyl halide of formula (III) is reacted with a condensed hydropyridyl compound of formula (IV), to give the compound of formula (Ic). This reaction may be carried out in the presence or absence of an inert solvent (preferably in the presence of an inert solvent) and in the presence or absence of a base (preferably in the presence of a base).

There is no specific limitation on the nature of the base employed, and any base known for use in reactions of this type may equally be used here. Examples of suitable bases include: organic amines, such as triethylamine, tributylamine, N-methylmorpholine, pyridine, 4-dimethylaminopyridine, picoline, lutidine, collidine, 1,8-diazabicyclo[5.4.0]undec-7-ene or 1,5-diazabicyclo[4.3.0]non-5-ene; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide or potassium t-butoxide; alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. Of these, the alkali metal carbonates are preferred. The amount of base employed is not critical, but we would generally recommend an amount of base of from an equimolar amount to 5 times the equimolar amount with respect to the starting material of formula (III). Where an excess of the starting material of formula (IV) is employed, this may also function as the base. Also, if an excess of an organic amine is employed as the base, this may additionally serve as the solvent.

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The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; ketones, such as acetone or methyl ethyl ketone; esters, such as ethyl acetate; alcohols, such as methanol, ethanol, propanol, isopropanol or butanol; nitriles, such as acetonitrile; amides, such as N,N-dimethylformamide, N,N-dimethyl acetamide, N-methyl-2-pyrrolidone or hexamethyl phosphoric triamide; and sulfoxides, such as dimethyl sulfoxide. Of these, the amides or the sulfoxides are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at from about room temperature to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

After completion of the reaction, the desired compound of formula (Ic) can be obtained from the reaction mixture by conventional means. For example, if the compound is produced immediately in the form of crystals, these can be separated simply by filtration. Alternatively, a suitable recovery procedure comprises: adding water; neutralizing the mixture, if necessary; extracting the mixture with a water-immiscible organic solvent; drying the extract; and distilling the solvent off. If necessary, the product thus obtained can be further purified by conventional means, such as recrystallization or the various chromatography techniques, for example preparative thin layer chromatography or column chromatography, notably column chromatography.

In the optional second step of this reaction, Step A2, the resulting compound of formula (Ic) is converted, if desired, to a compound of formula (I). This reaction may involve any one or more of the following reactions:

- (1) Where R^{3a} represents a hydroxy group, alkylation, aralkylation or acylation of this hydroxy group;
- (2) Where R^{3a} represents a nitro group, conversion of this nitro group to an amino group;
- (3) Alkylation, aralkylation or acylation of the amino group obtained as described in (2) above.

Alkylation, aralkylation or acylation of the hydroxy group in Step A2(1) is carried out in an inert solvent and in the presence of a base by reacting a hydroxy compound of formula (Ic) (R^{3a} represents a hydroxy group) with a corresponding alkylating, aralkylating or acylating agent, for example an alkyl halide, aralkyl halide, acyl halide or acid anhydride. The nature of this compound will, of course, depend on the nature of the group which it is desired to introduce into the compound of formula (I). However, examples of suitable compounds are as follows:

alkyl halides having from 1 to 4 carbon atoms, such as methyl iodide, ethyl bromide, ethyl iodide, propyl chloride, propyl bromide, butyl chloride or butyl iodide;

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aralkyl halides having from 7 to 14 carbon atoms, such as benzyl chloride, benzyl bromide, p-methylbenzyl chloride, p-methoxybenzyl chloride, p-chlorobenzyl chloride, p-fluorobenzyl chloride or naphthylmethyl chloride;

alkyl halides from 1 to 4 carbon atoms which are substituted by an alkoxy group having from 1 to 4 carbon atoms, by an alkanoyloxy group having from 1 to 6 carbon atoms or by an arylcarbonyloxy group having from 7 to 11 carbon atoms, such as methoxy methyl chloride, 1-methoxyethyl chloride, 2-methoxyethyl chloride, 1-methoxypropyl chloride, 1-methoxybutyl chloride, ethoxymethyl chloride, propoxymethyl chloride, butoxymethyl chloride, acetoxymethyl chloride, 1-acetoxyethyl chloride, 2-acetoxyethyl chloride, 1-acetoxypropyl chloride, 1-acetoxybutyl chloride, propionyloxymethyl chloride, butyryloxymethyl chloride, valeryloxymethyl chloride, pivaloyloxymethyl chloride, benzoyloxymethyl chloride, 1-benzoyloxyethyl chloride, p-methylbenzoyloxymethyl chloride, p-methoxybenzoyloxymethyl chloride, p-chlorobenzoyloxymethyl chloride, p-fluorobenzoyloxymethyl chloride or naphthoyloxymethyl chloride;

alkanoyl halides having from 2 to 18 carbon atoms or a mixed acid anhydride of one such corresponding acid with formic acid, such as acetyl chloride, propionyl chloride, butyryl chloride, butyryl bromide, valeryl chloride, isovaleryl chloride, pivaloyl chloride, hexanoyl chloride, nonanoyl chloride, decanoyl chloride, lauroyl chloride, palmitoyl chloride, stearoyl chloride, mixed acid anhydride of formic acid and acetic acid, acetic anhydride, propionic anhydride or butyric anhydride;

alkenoyl chlorides having from 3 to 6 carbon atoms, such as acryloyl chloride, methacryloyl chloride, crotonoyl chloride or 2-hexenoyl chloride;

cycloalkanecarbonyl halides having from 3 to 7 carbon atoms in the cycloalkane part, such as cyclopropanecarbonyl chloride, cyclobutanecarbonyl chloride, cyclopentanecarbonyl chloride, cyclohexanecarbonyl chloride or cycloheptanecarbonyl chloride;

arylcarbonyl halides having from 6 to 10 carbon atoms in the aryl part, such as benzoyl chloride, p-methylbenzoyl chloride, p-methoxybenzoyl chloride, p-chlorobenzoyl chloride, p-fluorobenzoyl chloride or naphthoyl chloride;

alkoxycarbonyl halides having from 1 to 4 carbon atoms in the alkoxy part, or an alkyl carbonate anhydride having from 1 to 4 carbon atoms in the alkyl part, such as methoxycarbonyl chloride, ethoxycarbonyl chloride, propoxycarbonyl chloride, isopropoxycarbonyl chloride, butoxycarbonyl chloride, t-butoxycarbonyl chloride, dimethyl dicarbonate, diethyl dicarbonate, dipropyl dicarbonate, diisopropyl dicarbonate, dibutyl dicarbonate or di-t-butyl dicarbonate;

aralkyloxycarbonyl halides having from 7 to 14 carbon atoms in the aralkyl part, such as benzyl oxycarbonyl chloride, p-methylbenzyloxycarbonyl chloride, p-methoxybenzyloxycarbonyl chloride, p-chlorobenzyloxycarbonyl chloride, p-fluorobenzyloxycarbonyl chloride or naphthylmethoxycarbonyl chloride;

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phthalidyl halides, such as phthalidyl chloride; or substituted methyl halides, such as (5-methyl- or 5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl chloride.

The base employed is not critical to the invention, provided that it has no adverse effect on other parts of the molecule, and any base commonly used in reactions of this type may equally be used here. Examples of suitable bases include: alkali metal hydrides, such as lithium hydride or sodium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide or potassium t-butoxide; alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. Of these, the alkali metal hydrides are preferred.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, tetrahydrofuran or dioxane; ketones, such as acetone or methyl ethyl ketone; esters, such as ethyl acetate; nitriles, such as acetonitrile; amides, such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide. Of these, the amides are preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C. to 100°C. (more preferably from 0°C. to 50°C.), although this may vary, depending on the nature of the compound of formula (Ic) and the solvent. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

The reaction of Step A2(2), which comprises the conversion of the nitro group represented by R^{3a} in the compound of formula (Ic) into an amino group is preferably effected, in an inert solvent and in the presence of an acid, by reaction of a nitro compound of formula (Ic) in which R^{3a} represents a nitro group with a reducing agent, for example a metal powder. Suitable reducing metal powders include powders of iron, tin or zinc. Of these, iron or tin powder is preferred.

Suitable acids include: mineral acids, such as hydrochloric acid or sulfuric acid; and organic acids, such as acetic acid, trifluoroacetic acid, methanesulfonic acid or p-toluenesulfonic acid. Of these, hydrochloric acid or acetic acid is preferred.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: water; ethers, such as diethyl ether, tetrahydrofuran or dioxane; alcohols, such as methanol or ethanol; the acid employed for the reaction, as mentioned above; or a mixture of any two or more of these

solvents. Of these, we prefer to use a mixture of water with an acid.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C. to 100°C. (more preferably from 0°C. to 50°C.), although this may vary depending on the nature of the starting material of formula (Ic) and on the solvent employed. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 15 minutes to 20 hours (more preferably from 30 minutes to 10 hours) will usually suffice. If this reaction is carried out in an organic acid and in the presence of one of the acid anhydrides mentioned later in connection with the reaction of Step A2(3), this reaction affords an amino-acylated compound.

Conversion of the nitro group into an amino group can be also conducted in a similar manner to Step C2(4) of Reaction Scheme C as described hereafter, and, in this case, any nitro group contained in R^1 is converted into an amino group at the same time.

Alkylation, aralkylation or acylation of the amino group can be conducted by reacting an amino compound of formula (Ic) in which R^3 represents an amino group with a corresponding alkyl halide, aralkyl halide, acyl halide or acid anhydride [for example: an alkyl halide having from 1 to 4 carbon atoms; an aralkyl halide having from 1 to 4 carbon atoms which is substituted by an alkoxy group having from 1 to 4 carbon atoms, by an alkanoyloxy group having from 1 to 6 carbon atoms or by an arylcarbonyloxy group having from 6 to 10 carbon atoms in the aryl moiety; an aralkyl halide having from 7 to 14 carbon atoms; an alkanoyl halide having from 2 to 18 carbon atoms or a mixed acid anhydride of a corresponding acid with formic acid; an alkenoyl halide having from 3 to 6 carbon atoms; a cycloalkanecarbonyl halide having from 3 to 7 carbon atoms in the cycloalkane moiety; an arylcarbonyl halide having from 6 to 10 carbon atoms in the aryl moiety; an alkoxy-carbonyl halide having from 1 to 4 carbon atoms in the alkoxy moiety; an alkyl carbonate anhydride having from 1 to 4 carbon atoms in the alkyl moiety; an aralkyloxycarbonyl halide having from 7 to 14 carbon atoms in the aralkyl moiety; a phthalidyl halide; or a (5-methyl or 5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl halide, all as exemplified above in relation to Step A2(1)]. This reaction normally and preferably takes place in an inert solvent and in the presence of a base. If it is desired to prepare a mono-alkylamino compound having from 1 to 4 carbon atoms, we prefer to use about an equimolar amount of an alkyl halide having from 1 to 4 carbon atoms with respect to the compound of formula (I); on the other hand, the desired compound is a di-alkylamino compound having from 1 to 4 carbon atoms in each alkyl moiety, it is preferred to use more than about 2 moles of an alkyl halide having from 1 to 4 carbon atoms per mole of the compound of formula (I).

The reaction is essentially the same as that employed in Step A1, and may be carried out using the reaction conditions, base and solvent as described above in relation to that reaction.

After completion of the reaction or any of the reactions described above, the desired compound can be

obtained from the reaction mixture by conventional means. For example, one suitable recovery procedure comprises: filtering off any insoluble matter; adding water to the filtrate; if necessary, neutralizing the resulting mixture; extracting it with a water-immiscible organic solvent, such as ethyl acetate; drying it; and distilling off the solvent. If necessary, the product thus obtained can be further purified by conventional means, such as recrystallization or the various chromatography techniques, for example preparative thin layer chromatography or column chromatography, notably column chromatography.

A salt of the compound of formula (I) can be prepared by conventional means, as is well known in the art. For example, the compound of formula (I) is treated with an acid, such as hydrochloric acid or maleic acid, in an inert solvent, such as diethyl ether or diisopropyl ether, and the separated crystals are recovered by filtration.

An optically active compound of formula (I) can be prepared by using a corresponding optically active benzyl halide of formula (II) as the starting material, or by optical resolution of a racemic compound of formula (I) by conventional means, such as fractional crystallization or liquid chromatography.

The condensed hydropyridyl compound of formula (IV), used as one of the starting materials, is known or may easily be prepared by any known method [for example, M. Podesta et al., *Eur. J. Med. Chem. - Chim. Ther.* 9 (5), 487-490 (1974); and Japanese Patent Kokai Application No. Sho 61-246186]. Compounds of formula (IV) having a nitro group as the group R^{3a} are known or can be prepared as follows:

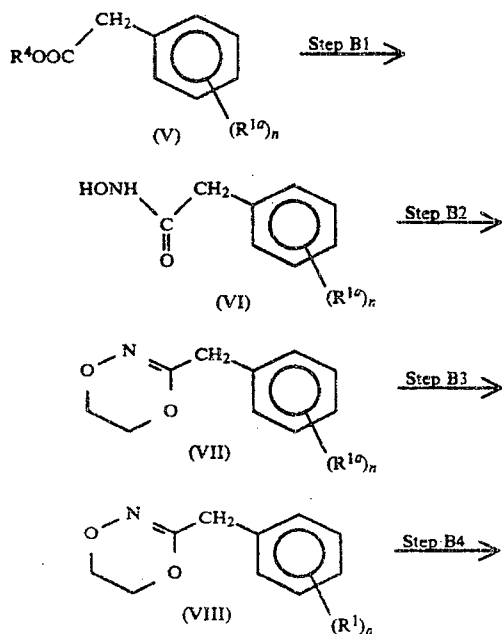
The imino group in a compound corresponding to the compound of formula (IV), but in which the group R^{3a} is a hydrogen atom [which can easily be prepared by any known method (for example as described in Japanese Patent Kokai Application No. Sho 62-103088)] is protected. The protecting reaction can be conducted in a similar way to that described in Step A2(3) of Reaction Scheme A, above. The protecting group may be, for example, an acyl group, such as an alkanoyl group having from 1 to 18 carbon atoms as exemplified above. The protected compound is then allowed to react in an inert solvent (which may be, for example, a fatty acid, such as acetic acid or propionic acid, or acid anhydride, such as acetic anhydride or propionic anhydride, or a mixture of any two or more thereof) with a nitrating agent (such as fuming nitric acid or anhydrous nitric acid) at a suitable temperature, for example from 0°C. to 50°C. , for a period of, for example, from 15 minutes to 5 hours, and is finally treated with an acid (such as aqueous hydrochloric acid or aqueous sulfuric acid) at a suitable temperature, for example from 20°C. to 100°C. , for a period of, for example, from 15 minutes to 5 hours to remove the protecting group.

The compound of formula (III), which is the other starting material, can easily be prepared, for example by the processes shown below in Reaction Schemes B, C, D and E.

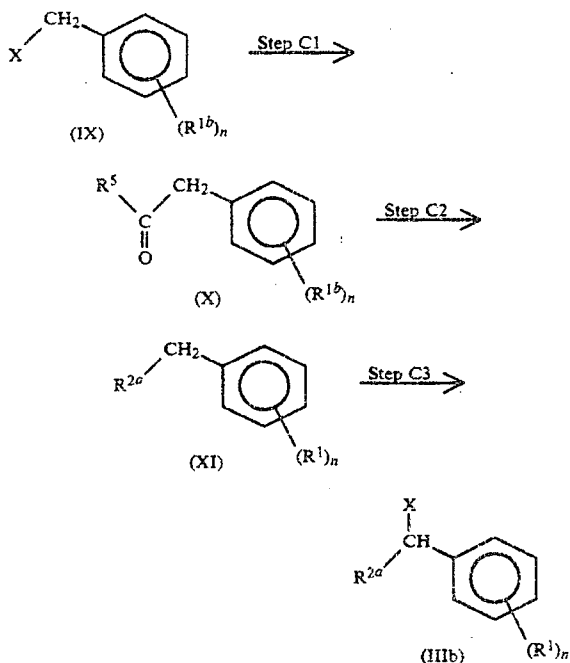
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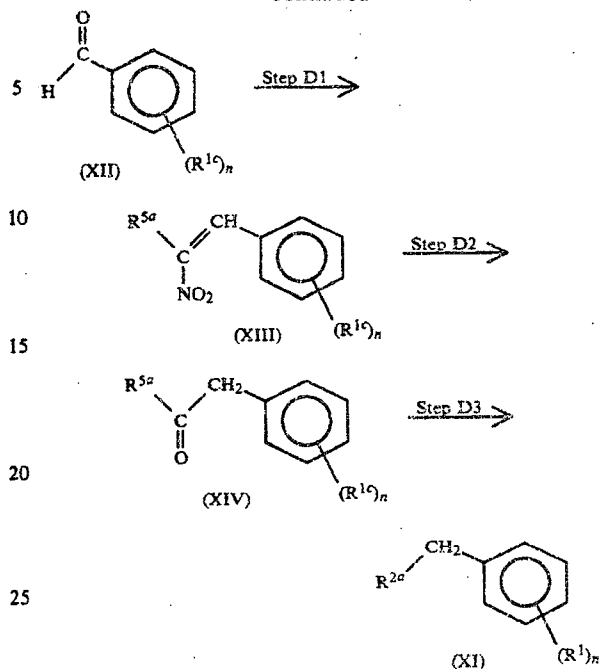
Reaction Scheme C:



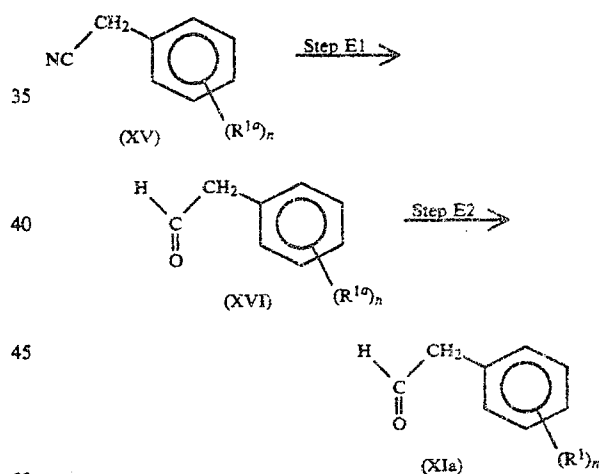
Reaction Scheme D:

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Reaction Scheme E:



In these formulae, R^1 , X and n are as defined above.

R^{1a} represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms in the alkanoyl part, a protected haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom in the haloalkanoyl part, a carbamoyl group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halo-

gen atom, or a sulfamoyl group. That is, it represents the same groups as does R¹, other than the cyano, carboxy and alkoxy, carbonyl, and the alkanoyl groups and the haloalkanoyl groups are protected.

R^{1b} represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a protected hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an protected alkanoyl group having from 1 to 5 carbon atoms in the alkanoyl part, a protected haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom in the haloalkanoyl part, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, or a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom. That is, it represents the same groups as does R¹, other than the amino, cyano, carboxy, carbamoyl, sulfamoyl and alkoxy carbonyl groups, and the alkanoyl groups, the haloalkanoyl groups and the hydroxy groups are protected.

R^{1c} represents the same groups as are defined above for R¹, except that the alkanoyl group having from 1 to 5 carbon atoms and the haloalkanoyl group having from 2 to 5 carbon atoms are protected.

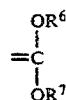
R^{2a} represents the same groups as are defined above for R², other than the dihydrodioxazinyl group.

R⁴ represents an alkyl group having from 1 to 4 carbon atoms.

R⁵ represents a hydrogen atom, an alkyl group having from 1 to 9 carbon atoms, a substituted alkyl group which has from 1 to 9 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined above, an alkenyl group having from 2 to 5 carbon atoms, a substituted alkenyl group which has from 2 to 5 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined above, a cycloalkyl group having from 3 to 7 carbon atoms, a substituted cycloalkyl group which has from 3 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined above, or a substituted phenyl group having at least one substituent selected from the group consisting of substituents B, defined above, and provided that any hydroxy group in substituents A is protected. That is, it represents any of the groups (other than the dihydrodioxazinyl group) defined above for R², but without the terminal carbonyl group.

R^{5a} represents any of the groups represented by R⁵, except that the hydroxy group of substituent A need not be protected.

There is no particular limitation on the nature of the protecting group for the alkanoyl group having from 1 to 5 carbon atoms or the haloalkanoyl group having from 2 to 5 carbon atoms, and any such group commonly used for the protection of aldehydes and ketones in the field of organic chemistry. Examples include an acetal or ketal containing a carbonyl moiety as shown in the following formula:



(XVII)

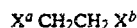
in which R⁶ and R⁷ are the same or different and each represents an alkyl group having from 1 to 4 carbon atoms (such as a methyl, ethyl, propyl, isopropyl or butyl group) or R⁶ and R⁷ together form an alkylene group having 2 or 3 carbon atoms (such as an ethylene or trimethylene group). We prefer an acetal or ketal in which R⁶ and R⁷ are each a methyl or ethyl group, or R⁶ and R⁷ together form an ethylene or trimethylene group.

The nature of the hydroxy-protecting groups which may be employed in this reaction is not critical and any hydroxy-protecting group known for use in this type of reaction may equally be employed here. Examples of such groups include groups derived from the cyclic ethers, such as the tetrahydropyranyl or tetrahydrofuranlyl group.

In Reaction Scheme B, a compound of formula (IIIa) is prepared; this is a compound of formula (III) in which R² is a dihydrodioxazinyl group.

In Step B1 of this Reaction Scheme, a compound of formula (VI) is prepared by reacting a compound of formula (V) with hydroxylamine or with a mineral acid salt of hydroxylamine (such as the hydrochloride or the sulfate) in an inert solvent (for example, an alcohol such as methanol or ethanol) and in the presence of a base (for example, an alkali metal alkoxide such as sodium methoxide, sodium ethoxide or potassium t-butoxide) at a suitable temperature, preferably from 0° C. to 150° C. (more preferably from about room temperature to 100° C.) for a suitable period, preferably from 1 to 24 hours (more preferably from 2 to 15 hours).

In Step B2 of this Reaction Scheme, a compound of formula (VII) is prepared by reacting a compound of formula (VI) with a compound of formula (XVIII):



(XVIII)

in which X^a and X^b are the same or different and each represents a halogen atom. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved, and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: water, and alcohols, such as methanol or ethanol. The reaction is also preferably effected in the presence of a base, the nature of which is also not critical to the present invention. Examples of such bases include: alkali metal carbonates, such as sodium carbonate or potassium carbonate; and alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the present invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at a temperature from about room temperature to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction

is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

Step B3 of this Reaction Scheme is optional to give a compound of formula (VIII), and may consist of one or more of the following reactions:

- (1) Removal of the alkanoyl or haloalkanoyl-protecting group contained in R^{1a};
- (2) Conversion of the halogen atom contained in R^{1a} into a cyano group;
- (3) Conversion of the halogen atom contained in R^{1a} into a carboxy group, followed, if desired, by conversion of the carboxy group into an alkoxy-carbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety.

In Step B3(1) of this Reaction Scheme, removal of the alkanoyl- or haloalkanoyl-protecting group can be effected by conventional means commonly employed in the field of organic chemistry. For example, if the protecting group is an acetal or a ketal, a corresponding compound of formula (VII) is reacted with an acid (for example, a mineral acid, such as hydrochloric acid, sulfuric acid or nitric acid; or an organic acid, such as acetic acid, trifluoroacetic acid, methanesulfonic acid or p-toluenesulfonic acid). The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: water and alcohols, such as methanol or ethanol. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 100° C. (more preferably at a temperature from about room temperature to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 10 minutes to 5 hours (more preferably from 30 minutes to 2 hours) will usually suffice.

Conversion of a halogen atom into a cyano group in Step B3(2) of this Reaction Scheme is preferably effected by reacting the corresponding compound of formula (VII) with a metal cyanide, such as sodium cyanide, potassium cyanide or copper cyanide. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: amides, such as dimethylformamide or dimethylacetamide; and ethers, such as diethyl ether or tetrahydrofuran. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at a temperature from about room temperature to 150° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under

the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

Conversion of the halogen atom into a carboxy group in Step B3(3) of this Reaction Scheme is preferably effected by reacting the corresponding compound of formula (VII) with magnesium. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether or tetrahydrofuran. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice. The resulting Grignard reagent is then reacted with carbon dioxide gas at a temperature from, for example, 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.) for a suitable period, for example from 30 minutes to 24 hours (more preferably from 1 to 10 hours).

Conversion of the resulting carboxy group into an alkoxy-carbonyl group having from 1 to 4 carbon atoms can, if desired, be conducted by reacting the corresponding carboxylic acid with an alcohol having from 1 to 4 carbon atoms, such as methanol, ethanol, propanol, isopropanol or butanol, in the presence of an acid (for example, a mineral acid, such as hydrochloric acid, sulfuric acid or nitric acid; or an organic acid, such as acetic acid, trifluoroacetic acid, methane sulfonic acid or p-toluenesulfonic acid). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 100° C. (more preferably at a temperature from about room temperature to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 5 hours (preferably from 1 to 2 hours) will usually suffice. Rather than using any additional solvent, this reaction is usually carried out by using as the solvent a large excess of the alcohol having from 1 to 4 carbon atoms, which is one of the reagents.

In Step B4, a compound of formula (IIIa) is prepared by reacting a compound of formula (VIII) with a haloimide, such as N-chlorosuccinimide, N-bromosuccinimide or N-iodosuccinimide in the presence of a radical initiator, such as benzoyl peroxide, or by reacting said compound of formula (VIII) with a halogen, such as chlorine, bromine or iodine, in an inert solvent (for example, a halogenated hydrocarbon, preferably a halogenated aliphatic hydrocarbon, such as methylene chloride, chloroform or carbon tetrachloride). The reaction can

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take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 100° C. (more preferably at a temperature from about room temperature to 50° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 20 hours (more preferably from 1 to 15 hours) will usually suffice.

In Reaction Scheme C, a compound of formula (IIIb) is prepared. This is a compound of formula (III) in which R² is replaced by R^{2a}, that is any of the groups defined above for R² except a dihydrodioxaziny group.

In Step C1 of this Reaction Scheme, a compound of formula (IX) is prepared by reacting a compound of formula (IX) with magnesium in an inert solvent (for example, an ether, such as diethyl ether or tetrahydrofuran), to give a Grignard reagent. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice. The resulting Grignard reagent is then reacted with a compound of formula (XIX), (XX) or (XXI):



or



in which R⁵ and X are as defined above; R^{5b} represents any of the groups defined for R⁵, except a group having a cyano substituent; and R^{5c} represents any of the groups defined for R⁵, except a hydrogen atom. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

Step C2 of Reaction Scheme C comprises one or more of the following optional reactions:

- (1) Removal of the alkanoyl or haloalkanoyl-protecting group contained in R^{1b};
- (2) Removal of the hydroxy-protecting group contained in R^{1b}, R⁵ etc;

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- (3) Conversion of the halogen atom contained in R^{1b} into a cyano group, and then optionally into a carbamoyl group, and then optionally into a carboxy, and finally optionally into an alkoxycarbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety;

- (4) Conversion of the nitro group contained in R^{1b} into an amino group; and

- (5) Conversion of the alkylthio group contained in R^{1b} into a sulfamoyl group.

Removal of the alkanoyl or haloalkanoyl-protecting group in Step C2(1) and removal of the hydroxy-protecting cyclic ether group in Step C2(2) can be conducted in a similar way to that in Step B3(1) of Reaction Scheme B, as described above.

Conversion of the halogen atom into a cyano group in Step C2(3) can be conducted in a similar way to that in Step B3(2) of Reaction Scheme B, as described above. In this reaction, it is preferred not to use as the starting material a compound of formula (X) containing a halogen atom in the substituent of R⁵. If a compound containing a halogen atom in the substituent R⁵ is used, conversion of this halogen atom into a cyano group is also possible.

Successive conversion of the cyano group into carbamoyl and carboxy groups can be conducted by reaction of a corresponding compound of formula (X) with an aqueous mineral acid (such as aqueous sulfuric acid, aqueous hydrochloric acid or aqueous nitric acid). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 200° C. (more preferably at a temperature from about room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice. In this reaction, it is possible to choose whether the carbamoyl or the carboxy compound will be obtained by adjusting the acid concentration. For example, the carbamoyl compound can be obtained by reaction in about 90% sulfuric acid, and then it can be converted into the carboxy compound by reaction in about 60% sulfuric acid.

Conversion of the carboxy group into an alkoxycarbonyl group having from 1 to 4 carbon atoms in the alkoxy moiety can be conducted in a similar way to that described in Step B3(3) of Reaction Scheme B, as described above.

Conversion of the nitro group into an amino group in Step C2(4) can be conducted by reacting the corresponding compound of formula (X) with hydrogen gas (preferably at from 1 atmosphere to 5 atmospheres) in an inert solvent (for example, an alcohol, such as methanol or ethanol) and in the presence of a reducing catalyst (such as Raney-nickel, palladium-on-carbon or platinum oxide). The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0° C. to 150° C. (preferably at room temperature to 100° C.). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and

solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

Conversion of the alkylthio group into a sulfamoyl group in Step C2(5) can be conducted by reacting a corresponding compound of formula (X) with a halogenating agent (such as chlorine or bromine) in an inert solvent (for example, water, an organic acid, such as acetic acid or propionic acid or a mixture of any two or more thereof), to give a sulfonyl halide. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -10°C . to 100°C . (more preferably at from 5°C . to 50°C .). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice. The resulting sulfonyl halide is then reacted with ammonia in an inert solvent (for example, water or an alcohol, such as methanol or ethanol) at, for example, from 0°C . to 100°C . (more preferably at room temperature to 50°C .) for a suitable period, for example from 30 minutes to 24 hours (more preferably from 1 to 10 hours).

In Step C3 of Reaction Scheme C, a compound of formula (IIIb) is prepared by halogenation of the compound of formula (XI) prepared in Step C2. This reaction is essentially the same as that described in Step B4 of Reaction Scheme B, and may be carried out using the same reagents and reaction conditions.

Reaction Scheme D provides an alternative route for preparing the compound of formula (XI), which is also prepared in Step C2 of Reaction Scheme C.

In Step D1 of Reaction Scheme D, a compound of formula (XIII) is prepared by reacting a compound of formula (XII) with a compound of formula (XXII):



in which R^{5a} is as defined above. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include organic acids, such as acetic acid or propionic acid. The reaction is also normally and preferably effected and in the presence of a base, for example, an ammonium salt of an organic acid, such as ammonium acetate, ammonium propionate or ammonium benzoate. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about room temperature to 200°C . (more preferably at from 50°C . to 150°C .). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

In Step D2 of Reaction Scheme D, a compound of formula (XIV) is prepared by reacting a compound of formula (XIII) with a reducing agent (such as zinc or iron) in an inert solvent (for example, an organic acid, such as acetic acid or propionic acid) and in the presence of water. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from about room temperature to 250°C . (more preferably at from 50°C . to 150°C .). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 30 minutes to 24 hours (more preferably from 1 to 10 hours) will usually suffice.

Step D3 of this Reaction Scheme is optional and comprises removal of the alkanoyl- or haloalkanoyl protecting group contained in R^{1c} . The removal reaction is essentially the same reaction as that employed in Step B3 of Reaction Scheme B, and may be carried out employing the same reagents and reaction conditions.

Reaction Scheme E provides an alternative route for preparing a compound of formula (XI), which is also prepared in Step C2 of Reaction Scheme C, when R^{2a} in the compound of formula (XI) is a formyl group, that is a compound of formula (XIa).

In Step E1 of Reaction Scheme E, a compound of formula (XVI) is prepared by reacting a compound of formula (XV) with a reducing agent [for example, an aluminum hydride, such as lithium tri(*t*-butoxy)aluminum hydride or lithium aluminum hydride]. The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include ethers, such as diethyl ether or tetrahydrofuran. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from -30°C . to 50°C . (more preferably at from 0°C . to room temperature). The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours (more preferably from 2 to 15 hours) will usually suffice.

Step E2 of Reaction Scheme E is optional and comprises one or more of the following reactions:

- (1) Removal of the alkanoyl or haloalkanoyl-protecting group contained in R^{1c} ;
- (2) Conversion of the halogen atom contained in R^{1c} into a cyano group, which may then, if desired, be converted into a carboxy group, which finally may, if desired, be converted into an alkoxycarbonyl group.

These reactions are essentially the same as those described above in relation to Step C2 of Reaction Scheme C, and may be carried out employing the same reagents and reaction conditions.

After completion of any of these reactions, the desired compound can be recovered from the reaction

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mixture by conventional means. For example, insoluble matter, if any, is filtered off, and, if the reaction solution is acidic or alkaline, the solution is neutralized. The desired product can then be recovered by distilling off the solvent, or by adding water, extracting the resulting mixture with a water-immiscible organic solvent, such as ethyl acetate, drying the extract, and then distilling off the solvent. If necessary, the product thus obtained can be further purified by conventional means, such as recrystallization or the various chromatography techniques, for example preparative thin layer chromatography or column chromatography, notably column chromatography.

Alternatively, when the desired compound is a carboxylic acid derivative, it may be recovered from the reaction medium by the following procedure: making the reaction solution alkaline; extracting the resulting mixture with a water-immiscible organic solvent, such as ethyl acetate; neutralizing the aqueous layer; extracting the desired compound with a water-immiscible organic solvent, such as ethyl acetate; drying the extract; and then distilling off the solvent.

The compounds of the present invention prepared as described above may be converted to acid addition salts and/or to complexes with metal ions by methods well known in the art.

BIOLOGICAL ACTIVITY

The compounds of formula (I) and their tautomers, salts and complexes of the present invention have an excellent inhibitory activity against blood platelet aggregation, and are therefore very useful for prevention and therapy of thrombosis and embolism. These activities are demonstrated by the following Test Examples, which employ techniques well recognized in the art to provide a model of such activity in humans and other mammals.

TEST EXAMPLE 1

Prolongation of Bleeding Time in mice

Male mice of the ICR strain (supplied by Japan Charles River Inc.) were divided into groups of 10 each for the test. A sample of the drug to be tested was suspended in a 5% w/v aqueous solution of gum arabic, and administered orally to the mice at a dose of 3 mg/kg for 3 successive days, namely 48 hours, 24 hours and 4 hours before the bleeding test. For the test, each of the mice was fixed by use of conventional apparatus, and the tail was cut 5 mm from the end. The last 2 cm of the tail was soaked in physiological saline kept warm at 37° C. The time at which bleeding was observed to cease for a successive 15 seconds was regarded as the point at which bleeding stopped, and the time between cutting the tail until the point when bleeding stopped was recorded as the bleeding time. The bleeding time was observed for a maximum of 5 minutes, and, even if bleeding continued for longer than 5 minutes, the bleeding time was reported as 5 minutes (300 seconds). The results are shown in Table 2. The test was carried out using certain of the compounds of the present invention, as well as with two prior art compounds.

Each of the compounds of the present invention is identified in the Table by the number assigned to it in the foregoing Table 1 and by the number of the Example hereafter which illustrates its preparation. The prior art compounds are identified as follows:

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Compound A: 5 (2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

Compound B: 5-(2-chloro- α -methoxycarbonylbenzyl) 4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

TEST EXAMPLE 2

Inhibition of Blood Platelet Aggregation

Female rats of the SD strain (supplied by Japan Charles River Inc.) were divided into groups of 4 each for the test. A sample of the drug to be tested was suspended in a 5% w/v aqueous solution of gum arabic, and administered orally to the rats 4 hours before the test. As a control, a 5% w/v aqueous solution of gum arabic was administered to a control group of rats, without any test drug. Blood platelet aggregation was tested according to the method of P. Lumley and P. P. A. Humphrey [J. Pharmacol. Methods 6, 153-166 (1981)] with a partial modification. From the abdominal aorta of the anesthetized rat, 5.4 ml of a blood sample was taken in 0.6 ml of a 3.8% (w/v) sodium citrate solution serving as an anticoagulant. The resulting citrate-containing blood samples were poured into cuvettes, with 1.2 ml in each cuvette, and stirred (1000 rpm) at 37° C. After preliminary heating for 2 minutes, 0.3 ml of the blood sample was taken out of each of the cuvettes, and the blood platelet count was measured by means of an automatic blood cell counter (E-4000, Sysmex); this was regarded as the blood platelet count before addition. 0.9 ml of the blood sample in the cuvette was then mixed with 0.1 ml of a 0.05M adenosine diphosphate (ADP) solution or with 0.1 ml of a collagen suspension (0.06 mg/ml), to induce blood platelet aggregation. Two minutes after addition of the ADP, or 4 minutes after addition of the collagen, 0.3 ml of the blood sample was taken and the blood platelet count was measured; this was regarded as the blood platelet count after addition. The blood platelet aggregation rate was calculated from the following equation.

$100 \times (\text{blood platelet count before addition} - \text{blood platelet count after addition}) / \text{blood platelet count before addition}$

The inhibitory effect was calculated as the percent inhibition of the treated groups as compared with the control groups. The results are reported in Table 2.

TABLE 2

Ex. No.	Cpd. No.	Test Ex. 1 Bleeding time (hours)		Test Ex. 2 % Inhibition	
		3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
5	60	2.20	—	74.2	100
6	19	2.13	—	29.3	97.8
12	59	>2.75	57.1	98.1	—
20	235	>2.75	98.8	—	—
22	233	2.30	—	—	98.9
23	190	>2.75	100	—	—
25	194	>2.75	100	—	—
26	196	>2.75	97.6	—	—
Compound A		1.00	—	—	3.7*
Compound B		1.80	—	25.7	98.8

*at a dose of 30 mg/kg.

For therapeutic or prophylactic use, the compounds of the present invention may be administered by themselves or in admixture with any one or more conventional carriers, diluents or additives. Administration may be by any convenient route, for example orally or parenterally, and the formulation will be chosen having regard to the intended route of administration. The

compounds may, for example, be administered in the form of powders, granules, tablets, capsules and injections. The dosage may vary depending upon the severity and nature of the disorder, as well as the symptoms, age and body weight of the patient and the chosen route of administration; however, in the case of oral administration, we would normally suggest a dose of from 1 to 1000 mg, more preferably from 10 to 500 mg, if administered orally, or a dose of from 0.5 to 500 mg, more preferably from 5 to 250 mg, if administered intravenously. The compound may be administered in single or divided doses, e.g. from 1 to 3 times a day depending on the symptoms.

The preparation of the compounds of the present invention is further illustrated by the following non-limiting Examples, whilst the preparation of certain of the starting materials used in these Examples is illustrated by the subsequent Preparations.

EXAMPLE 1

5-(2-Chloro- α -trifluoroacetylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 113)

10 ml of methylene chloride were added to 0.39 g (2.6 mmole) of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and 0.28 g (2.6 mmole) of sodium carbonate, and then a solution of 0.67 g (2.2 mmole) of 2-chloro- α -trifluoroacetylbenzyl bromide in 10 ml of methylene chloride was slowly added to the resulting mixture, whilst stirring at room temperature. The mixture was then stirred at room temperature for 3 hours. At the end of this time, 200 ml of ethyl acetate were added to the reaction mixture, and the organic layer was separated, washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed by distillation under reduced pressure, and the resulting residue was subjected to silica gel column chromatography, using a 100:4 by volume mixture of toluene and ethyl acetate as the eluent, to give 0.31 g of the title compound as a colorless oil.

Infrared Absorption Spectrum (thin film) $\nu_{\max}$ cm⁻¹: 1685, 1705.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 2.90–3.04 (2H, multiplet); 3.90 (1H, triplet, J=6.0 Hz); 4.01 (1H, triplet, J=6.0 Hz); 5.51 (1H, doublet, J=7.3 Hz); 5.58 (1H, doublet, J=7.3 Hz); 6.82 (1H, doublet, J=5.4 Hz); 7.19 (2H, doublet, J=5.4 Hz); 7.36–7.58 (4H, multiplet).

Mass spectrum (CI, m/z): 360 (M⁺+1). Here and hereafter, in the mass spectra, "CI" means "chemical ionization".

EXAMPLE 2

5-[2-Chloro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 3)

2(a) Following a procedure similar to that described in Example 1, except that an equivalent amount of 2-chloro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide (prepared as described in Preparation 18) was used in place of the 2-chloro- α -trifluoroacetylbenzyl bromide, the title compound was obtained as a colorless oil in a yield of 77%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 2.77–2.94 (4H, multiplet); 3.63 (1H, doublet, J=14.4 Hz); 3.79 (1H, doublet, J=14.4 Hz); 3.96–4.02 (1H, multiplet); 4.08–4.14 (1H, multiplet); 4.27–4.32 (1H, multiplet); 4.36–4.42 (1H, multiplet); 4.75 (1H,

singlet); 6.70 (1H, doublet, J=5.4 Hz); 7.07 (1H, doublet, J=5.4 Hz); 7.20–7.90 (4H, multiplet).

Mass spectrum (CI, m/z): 349 (M⁺+1).

2(b) 2.7 g of the title compound obtained as described in step (a) above were dissolved in 100 ml of diethyl ether, and hydrogen chloride gas was blown into the resulting solution at room temperature. The crystals which precipitated were collected to obtain 2.3 g of the hydrochloride of the title compound as a colorless powder, melting at 104°–107° C.

Elemental analysis: Calculated for C₁₇H₁₇ClN₂O₂S.HCl.3/2H₂O: C, 49.52%; H, 5.13%; N, 6.80%. Found: C, 49.81%; H, 4.73%; N, 6.56%.

EXAMPLE 3

5-[2-Fluoro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 2)

3(a) Following a procedure similar to that described in Example 1, except that an equivalent amount of 2-fluoro-(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide (prepared as described in Preparation 19) was used in place of the 2-chloro- α -trifluoroacetylbenzyl bromide, the title compound was obtained as a colorless oil in a yield of 50%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 2.73–2.98 (4H, multiplet); 3.63 (1H, doublet, J=13.8 Hz); 3.79 (1H, doublet, J=13.8 Hz); 3.95–4.18 (2H, multiplet); 4.23–4.45 (H, multiplet); 4.61 (1H, singlet); 6.70 (1H, doublet, J=5.4 Hz); 7.09 (1H, doublet, J=5.4 Hz); 7.20–7.80 (4H, multiplet).

Mass spectrum (CI, m/z): 333 (M⁺+1).

3(b) The procedure described in Example 2(b) was repeated, using the title compound as prepared in step (a) above, to obtain the hydrochloride of the title compound as a colorless powder, melting at 108°–112° C., in a yield of 81%.

Elemental analysis: Calculated for C₁₇H₁₇FN₂O₂S.HCl.H₂O: C, 52.78%; H, 5.21%; N, 7.24%. Found: C, 53.19%; H, 4.99%; N, 7.16%.

EXAMPLE 4

5-[2,6-Difluoro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 7)

Following a procedure similar to that described in Example 1, except that an equivalent amount of 2,6-difluoro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide (prepared as described in Preparation 20) was used in place of the 2-chloro- α -trifluoroacetylbenzyl bromide, the title compound was obtained as a colorless powder, melting at 151°–153° C., in a yield of 8%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 2.81–2.93 (4H, multiplet); 3.62 (1H, doublet, J=14.0 Hz); 3.79 (1H, doublet, J=14.0 Hz); 4.00–4.10 (2H, multiplet); 4.26–4.36 (2H, multiplet); 4.59 (1H, singlet); 6.70 (1H, doublet, J=5.4 Hz); 7.08 (1H, doublet, J=5.4 Hz); 7.20–7.80 (4H, multiplet).

Mass spectrum (CI, m/z): 351 (M⁺+1).

Elemental analysis: Calculated for C₁₇H₁₆F₂N₂O₂S: C, 58.27%; H, 4.60%; N, 8.00%. Found: C, 58.22%; H, 4.61%; N, 7.79%.

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EXAMPLE 5

5-(2-Chloro- α -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its sulfate (Compound No. 60)

5(a) Following a procedure similar to that described in Example 1, except that an equivalent amount of 2-chloro- α -cyclopropylcarbonylbenzyl bromide was used in place of the 2-chloro- α -trifluoroacetylbenzyl bromide, the title compound was obtained as a yellow oil in yield of 66%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.78–0.90 (2H, multiplet); 0.96–1.06 (2H, multiplet); 2.15–2.29 (1H, multiplet); 2.83–2.94 (4H, multiplet); 3.56 (1H, doublet, $J=4.3$ Hz); 3.72 (1H, doublet, $J=4.3$ Hz); 5.06 (1H, singlet); 6.68 (1H, doublet, $J=4.9$ Hz); 7.06 (1H, doublet, $J=4.9$ Hz); 7.10–7.70 (4H, multiplet).

Mass spectrum (CI, m/z): 332 ($M^+ + 1$), 262.

5(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound as prepared in step (a) above, except that concentrated sulfuric acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the sulfate of the title compound as white crystals, melting at 184° – 186° C., in a yield of 70%.

Elemental analysis: Calculated for $\text{C}_{18}\text{H}_{18}\text{ClNOS} \cdot \text{H}_2\text{SO}_4$: C, 50.28%; H, 4.69%; N, 3.26%; Found: C, 50.43%; H, 4.53%; N, 2.87%.

EXAMPLE 6

5-(2-Fluoro- α -propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 19)

6(a) 1.85 g (11.13 mmole) of 1-(2-fluorophenyl)-2-butanone (prepared as described in Preparation 9) were dissolved in 30 ml of carbon tetrachloride, and then a solution of 1.78 g of bromine in 15 ml of carbon tetrachloride was added dropwise to the resulting solution at room temperature over a period of 30 minutes. The resulting mixture was then stirred at room temperature for 5 hours, after which water was added to the reaction mixture. The reaction mixture was then extracted with chloroform, and the extract was dried over anhydrous magnesium sulfate. A crude 2-fluoro- α -propionylbenzyl bromide was obtained from this extract by removal of the solvent by evaporation under reduced pressure. 1.95 g (11.13 mmole) of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, 3.38 g (24.45 mmole) of anhydrous potassium carbonate and 30 ml of dimethylformamide were added to the crude product thus obtained, and the resulting mixture was stirred at room temperature for 5 hours. At the end of this time, toluene was added to the reaction mixture, and after the insolubles had been removed by filtration, the filtrate was concentrated by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, using a 19:1 by volume mixture of toluene and ethyl acetate as the eluent, to give 1.17 g of the title compound as a pale yellow oil.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1} : 1715.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 1.03 (3H, triplet, $J=7.0$ Hz); 2.50 (2H, quartet, $J=7.0$ Hz); 2.80–2.95 (4H, multiplet); 3.53 (1H, doublet, $J=11.0$ Hz); 3.63 (1H, doublet, $J=11.0$ Hz); 4.75 (1H,

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singlet); 6.67 (1H, doublet, $J=5.7$ Hz); 7.05 (1H, doublet, $J=5.7$ Hz); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 304 ($M^+ + 1$), 246.

6(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the reaction mixture, to obtain the maleate of the title compound as a colorless powder, melting at 101° – 103° C., in a yield of 54%.

Elemental analysis: Calculated for $\text{C}_{17}\text{H}_{18}\text{FNOS} \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 58.86%; H, 5.41%; N, 3.27%; Found: C, 59.19%; H, 5.33%; N, 3.19%.

EXAMPLE 7

5-(α -Acetyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 10)

7(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-chlorophenyl)-2-propanone (prepared as described in Preparation 10) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 44%.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1} : 1715.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 2.13 (3H, singlet); 2.70–2.95 (4H, multiplet); 3.50 (1H, doublet, $J=10.0$ Hz); 3.70 (1H, doublet, $J=10.0$ Hz); 4.93 (1H, singlet); 6.65 (1H, doublet, $J=5.7$ Hz); 7.05 (1H, doublet, $J=5.7$ Hz); 7.10–7.75 (4H, multiplet).

Mass spectrum (CI, m/z): 306 ($M^+ + 1$), 262.

7(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a pale yellow powder, melting at 98° – 101° C., in a yield of 70%.

Elemental analysis: Calculated for $\text{C}_{16}\text{H}_{16}\text{ClNOS} \cdot \text{HCl} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 54.70%; H, 5.16%; N, 3.98%; Found: C, 55.09%; H, 4.97%; N, 3.80%.

EXAMPLE 8

5-(2-Chloro- α -propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 20)

8(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of (2-chlorophenyl)-2-butanone (prepared as described in Preparation 11) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 32%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 1.05 (3H, triplet, $J=6.5$ Hz); 2.31–2.58 (2H, multiplet); 2.75–3.00 (4H, multiplet); 3.48 (1H, doublet, $J=14.5$ Hz); 3.68 (1H, doublet, $J=14.5$ Hz); 4.97 (1H, singlet); 6.65 (1H, doublet, $J=6.0$ Hz); 7.05 (1H, doublet, $J=6.0$ Hz); 7.10–7.65 (4H, multiplet).

Mass spectrum (CI, m/z): 320 ($M^+ + 1$).

8(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a pale yellow powder, melting at 110° – 115° C., in a yield of 25%.

Elemental analysis: Calculated for $\text{C}_{17}\text{H}_{18}\text{ClNOS} \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 54.55%; H, 5.92%; N, 3.74%; Found: C, 54.39%; H, 5.59%; N, 3.73%.

EXAMPLE 9

5-(2-Chloro- α -hexanoylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 125)

Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-chlorophenyl)-2-heptanone (prepared as described in Preparation 12) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a yellow oil in a yield of 10%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.90 (3H, triplet, $J=7.6$ Hz); 1.10–1.60 (6H, multiplet); 2.40 (2H, triplet, $J=8.0$ Hz); 2.75–3.00 (4H, multiplet); 3.50 (1H, doublet, $J=14.5$ Hz); 3.70 (1H, doublet, $J=14.5$ Hz); 5.00 (1H, singlet); 6.65 (1H, doublet, $J=6.0$ Hz); 7.05 (1H, doublet, $J=6.0$ Hz); 7.10–7.60 (4H, multiplet).

Mass spectrum (CI, m/z): 362 ($M^+ + 1$), 262.

EXAMPLE 10

5-(α -Acetyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 9)

10(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-2-propanone was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 55%.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1} : 1715.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 2.18 (3H, singlet); 2.80–2.95 (4H, multiplet); 3.55 (1H, doublet, $J=12.0$ Hz); 3.65 (1H, doublet, $J=12.0$ Hz); 4.72 (1H, singlet); 6.65 (1H, doublet, $J=5.5$ Hz); 7.05 (1H, doublet, $J=5.5$ Hz); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 290 ($M^+ + 1$), 246.

10(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a pale yellow powder, melting at 104°–106° C., in a yield of 61%.

Elemental analysis: Calculated for $\text{C}_{16}\text{H}_{16}\text{FNOS} \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 57.96%; H, 5.10%; N, 3.38%; Found: C, 58.36%; H, 4.94%; N, 3.39%.

EXAMPLE 11

5-(α -Cyclobutylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 106)

11(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of cyclobutyl-2-fluorobenzyl ketone (prepared as described in Preparation 13) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 24%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 1.70–2.55 (6H, multiplet); 2.80–3.00 (4H, multiplet); 3.50 (1H, doublet, $J=11.0$ Hz); 3.62 (1H, doublet, $J=11.0$ Hz); 3.70–3.90 (1H, multiplet); 4.73 (1H, singlet); 6.65 (1H, doublet, $J=6.0$ Hz); 7.05 (1H, doublet, $J=6.0$ Hz); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z): 330 ($M^+ + 1$), 246.

11(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride

gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 99°–104° C., in a yield of 57%.

Elemental analysis: Calculated for $\text{C}_{16}\text{H}_{16}\text{FNOS} \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 60.78%; H, 5.54%; N, 3.08%; Found: C, 60.97%; H, 5.48%; N, 2.94%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 1.70–2.30 (6H, multiplet); 3.10–3.30 (4H, multiplet); 3.68–3.82 (1H, multiplet); 4.30 (2H, broad singlet); 5.55 (1H, singlet); 6.30 (2H, singlet); 6.72 (1H, doublet, $J=6.5$ Hz); 7.20 (1H, doublet, $J=6.5$ Hz); 7.25–7.60 (4H, multiplet).

EXAMPLE 12

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 59)

12(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of cyclopropyl 2-fluorobenzyl ketone (prepared as described in Preparation 8) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a colorless oil in a yield of 69%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.78–0.90 (2H, multiplet); 0.98–1.11 (2H, multiplet); 2.22–2.34 (1H, multiplet); 2.72–2.98 (4H, multiplet); 3.58 (1H, doublet, $J=4.2$ Hz); 3.68 (1H, doublet, $J=4.2$ Hz); 4.85 (1H, singlet); 6.68 (1H, doublet, $J=4.9$ Hz); 7.06 (1H, doublet, $J=4.9$ Hz); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z): 316 ($M^+ + 1$), 246.

12(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 171°–173° C., in a yield of 75%.

Elemental analysis: Calculated for $\text{C}_{18}\text{H}_{18}\text{FNOS} \cdot \text{HCl}$: C, 61.44%; H, 5.44%; N, 3.98%; Found: C, 61.37%; H, 5.74%; N, 3.85%.

EXAMPLE 13

5-(α -Butyryl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 116)

13(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-2-pentanone (prepared as described in Preparation 5) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 41%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.82 (3H, triplet, $J=9.5$ Hz); 1.45–1.70 (2H, multiplet); 2.41 (2H, triplet, $J=8.0$ Hz); 2.75–2.95 (4H, multiplet); 3.55 (1H, doublet, $J=13.0$ Hz); 3.62 (1H, doublet, $J=13.0$ Hz); 4.75 (1H, singlet); 6.65 (1H, doublet, $J=6.0$ Hz); 7.05 (1H, doublet, $J=6.0$ Hz); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 318 ($M^+ + 1$), 246.

13(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 89°–90° C., in a yield of 36%.

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Elemental analysis: Calculated for $C_{18}H_{20}FNOS \cdot C_4H_4O_4$: C, 60.96%; H, 5.58%; N, 3.23%; Found: C, 60.69%; H, 5.43%; N, 3.01%.

EXAMPLE 14

5-(2-Fluoro- α -valerylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 120)

14(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-2-hexanone (prepared as described in Preparation 6) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 46%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.83 (3H, triplet, $J=8.0$ Hz); 1.12-1.35 (2H, multiplet); 1.40-1.70 (2H, multiplet); 2.45 (2H, triplet, $J=8.2$ Hz); 2.60-2.90 (4H, multiplet); 3.52 (1H, doublet, $J=14.0$ Hz); 3.65 (1H, doublet, $J=14.0$ Hz); 4.75 (1H, singlet); 6.65 (1H, doublet, $J=6.0$ Hz); 7.05 (1H, doublet, $J=6.0$ Hz); 7.10-7.50 (4H, multiplet).

Mass Spectrum (CI, m/z): 332 ($M^+ + 1$), 246.

14(b) A procedure similar to that described in Example (b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 92° - 93° C., in a yield of 26%.

Elemental analysis: Calculated for $C_{19}H_{22}FNOS \cdot C_4H_4O_4$: C, 61.73%; H, 5.86%; N, 3.13%; Found: C, 61.38%; H, 5.88%; N, 2.59%.

EXAMPLE 15

5-(2-Fluoro- α -pivaloylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 122)

15(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 1-(2-fluorophenyl)-3,3-dimethyl-2-butanone (prepared as described in Preparation 7) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 87%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.10 (9H, singlet); 2.74-3.00 (4H, multiplet); 3.55 (1H, doublet, $J=15.0$ Hz); 3.66 (1H, doublet, $J=15.0$ Hz); 5.23 (1H, singlet); 6.63 (1H, doublet, $J=6.0$ Hz); 7.03 (1H, doublet, $J=6.0$ Hz); 7.10-7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 332 ($M^+ + 1$), 246.

15(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a pale yellow powder, melting at 85° - 90° C., in a yield of 34%.

Elemental analysis: Calculated for $C_{19}H_{22}FNOS \cdot HCl \cdot H_2O$: C, 59.14%; H, 6.23%; N, 3.63%; Found: C, 58.99%; H, 6.57%; N, 3.17%.

EXAMPLE 16

5-[2-Chloro- α -(4-fluorobenzoyl)benzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 149)

16(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 2-chlorobenzyl 4-fluorophenyl ketone (prepared as described in Preparation 22) was used in place of the 1-(2-

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fluorophenyl)-2-butanone, the title compound was obtained as a pale yellow oil in a yield of 58%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.80-3.00 (4H, multiplet); 3.63 (1H, doublet, $J=16.0$ Hz); 3.80 (1H, doublet, $J=16.0$ Hz); 5.80 (1H, singlet); 6.63 (1H, doublet, $J=6.0$ Hz); 7.00-7.60 (6H, multiplet); 7.95-8.15 (2H, multiplet).

Mass spectrum (CI, m/z): 386 ($M^+ + 1$), 262.

16(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as a yellowish brown powder, melting at 121° - 130° C., in a yield of 40%.

Elemental analysis: Calculated for $C_{21}H_{17}ClFNOS \cdot HCl \cdot \frac{1}{2}H_2O$: C, 58.47%; H, 4.44%; N, 3.25%; Found: C, 58.25%; H, 4.86%; N, 3.48%.

EXAMPLE 17

5-(2-Fluoro- α -isobutyrylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its maleate (Compound No. 118)

17(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of 2-fluorobenzyl isopropyl ketone (prepared as described in Preparation 23) was used in place of the 1-(2-fluorophenyl)-2-butanone, the title compound was obtained as a yellow oil in a yield of 44%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.95 (3H, doublet, $J=7.0$ Hz); 1.10 (3H, doublet, $J=7.0$ Hz); 2.60-2.80 (1H, multiplet); 2.80-2.95 (4H, multiplet); 3.50 (1H, doublet, $J=11.0$ Hz); 3.65 (1H, doublet, $J=11.0$ Hz); 4.90 (1H, singlet); 6.65 (1H, doublet, $J=5.7$ Hz); 7.05 (1H, doublet, $J=5.7$ Hz); 7.10-7.50 (4H, multiplet).

Mass spectrum (CI, m/z): 318 ($M^+ + 1$), 246.

17(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that maleic acid was added in place of blowing hydrogen chloride gas through the mixture, to obtain the maleate of the title compound as a colorless powder, melting at 96° - 98° C., in a yield of 42%.

Elemental analysis: Calculated for $C_{18}H_{20}FNOS \cdot C_4H_4O_4$: C, 61.02%; H, 5.59%; N, 3.23%; Found: C, 60.74%; H, 5.52%; N, 3.23%.

EXAMPLE 18

5(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 175)

18(a) Following a procedure similar to that described in Example 6, except that an equivalent amount of cyclopropyl 2-fluorobenzyl ketone (prepared as described in Preparation 8) was used in place of the 1-(2-fluorophenyl)-2-butanone and that 2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (prepared as described in Preparation 24) was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, the title compound was obtained as a brown oil in a yield of 72%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.82-0.92 (2H, multiplet); 1.01-1.11 (2H, multiplet); 2.00-2.20 (1H, multiplet); 2.75-3.05 (4H, multiplet); 3.61 (2H, singlet); 4.91 (1H, singlet); 7.10-7.45 (4H, multiplet); 7.55 (1H, singlet).

Mass spectrum (CI, m/z): 361 ($M^+ + 1$), 291.

18(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 161°–168° C., in a yield of 79%.

Elemental analysis: Calculated for $C_{18}H_{17}FN_2O_3 \cdot S \cdot HCl$: C, 54.47%; H, 4.57%; N, 7.06%. Found: C, 54.47%; H, 4.63%; N, 6.89%.

EXAMPLE 19

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrofuro[3,2-c]pyridine and its hydrochloride (Compound No. 168)

19(a) Following a procedure similar to that described in Example 12, except that an equivalent amount of 4,5,6,7-tetrahydrofuro[3,2-c]pyridine (prepared as described in Preparation 25) was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, the title compound was obtained as a brown oil in a yield of 21%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–0.95 (2H, multiplet); 0.98–1.10 (2H, multiplet); 2.15–2.31 (1H, multiplet); 2.65–3.05 (4H, multiplet); 3.40–3.60 (2H, multiplet); 4.90 (1H, singlet); 6.15 (1H, doublet, $J=5.0$ Hz); 7.05–7.55 (5H, multiplet).

Mass spectrum (CI, m/z): 300 ($M^+ + 1$), 230.

19(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 154°–155° C., in a yield of 39%.

Elemental analysis: Calculated for $C_{18}H_{18}FNO_2 \cdot HCl$: C, 64.38%; H, 5.70%; N, 4.17%. Found: C, 64.37%; H, 5.80%; N, 4.19%.

EXAMPLE 20

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 235)

20(a) Following a procedure similar to that described in Example 12, except that an equivalent amount of 2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrochloride was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, the title compound was obtained as a brown oil in a yield of 32%. Diisopropyl ether was added to this compound to cause crystallization, yielding white crystals, melting at 123°–125° C.

The resulting 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 235) is believed to contain a small quantity of the tautomeric 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 188), from which it was not separated.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–0.96 (2H, multiplet); 0.99–1.14 (2H, multiplet); 1.83–2.01 (1H, multiplet); 2.02–2.17 (1H, multiplet); 2.25–2.45 & 2.47–2.62 (together 2H, each multiplet); 2.85 & 3.10 (together 2H, each doublet, $J=12.0$ Hz); 3.88–4.01 & 4.03–4.16 (together 2H, each multiplet); 4.85 & 4.89 (together 1H, each singlet); 6.03 & 6.06 (together 1H, each singlet); 7.10–7.45 (4H, multiplet).

Mass spectrum (CI, m/z): 332 ($M^+ + 1$), 262.

Elemental analysis: Calculated for $C_{18}H_{18}FNO_2 \cdot S$: C, 65.23%; H, 5.48%; N, 4.23%. Found: C, 65.09%; H, 5.55%; N, 4.20%.

20(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 104°–109° C., in a yield of 46%.

EXAMPLE 21

5-(2-Fluoro- α -propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 234)

21(a) Following a procedure similar to that described in Example 20, except that an equivalent amount of 1-(2-fluorophenyl)-2-butanone (prepared as described in Preparation 9) was used in place of the cyclopropyl 2-fluorobenzyl ketone, the title compound was obtained as a brown oil in a yield of 36%.

The resulting 5-(2-fluoro- α -propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 234) is believed to contain a small quantity of the tautomeric 5-(2-fluoro- α -propionylbenzyl)-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 187).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.00 (3H, triplet, $J=9.1$ Hz); 1.82–1.98 (1H, multiplet); 2.25–2.50 (4H, multiplet); 2.85 & 3.05 (together 2H, each doublet, $J=14.0$ Hz); 3.84–3.95 & 4.04–4.17 (together 2H, each multiplet); 4.72 & 4.76 (together 1H, each singlet); 6.03 & 6.07 (together 1H, each singlet); 7.15–7.40 (4H, multiplet).

Mass spectrum (CI, m/z): 320 ($M^+ + 1$), 262.

21(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, to obtain the hydrochloride of the title compound as white crystals, melting at 110°–115° C. in a yield of 78%.

EXAMPLE 22

5-(2-Chloro- α -cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 233)

Following a procedure similar to that described in Example 5, except that an equivalent amount of 2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrochloride was used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride, a yellow oil was obtained. The oil was crystallized from diisopropyl ether to give the title compound as pale brown crystals, melting at 119°–123° C. in a yield of 8%.

The resulting 5-(2-chloro- α -cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 233) is believed to contain a small quantity of the tautomeric 5-(2-chloro- α -cyclopropylcarbonylbenzyl)-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 186).

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.75–1.10 (4H, multiplet); 1.75–2.10 (2H, multiplet); 2.25–2.70 (2H, multiplet); 2.90–3.30 (2H, multiplet); 3.75–4.20 (2H, multiplet); 5.09 & 5.10 (together 1H, each singlet); 5.98 & 6.07 (together 1H, each singlet); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z): 348 ($M^+ + 1$), 278.

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EXAMPLE 23

2-Acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 190)

2.6 g (7.8 mmole) of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine pyridine (prepared as described in Example 20) were dissolved in a mixture of 10 ml of dimethylformamide and 5 ml of acetic anhydride, and then 0.35 g (8.6 mmole) of a 60% w/w dispersion of sodium hydride in mineral oil was added to the resulting solution, whilst ice-cooling; the mixture was then stirred for 20 minutes at the same temperature, after which it was stirred for a further 3 hours at room temperature. At the end of this time, 300 ml of ethyl acetate were added to the mixture, which was then washed four times, each time with 50 ml of a saturated aqueous solution of sodium chloride. The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, using a 100:3 by volume mixture of toluene and ethyl acetate as the eluent, to give a yellow oil. This oil was crystallized from diisopropyl ether, to obtain the title compound as white crystals, melting at 120°–121.5° C., in a yield of 65%.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹: 1758, 1704.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.80–0.95 (2H, multiplet); 0.99–1.16 (2H, multiplet); 2.27 (3H, singlet); 2.21–2.34 (1H, multiplet); 2.70–2.95 (4H, multiplet); 3.47 (1H, doublet, J=15.0 Hz); 3.57 (1H, doublet, J=15.0 Hz); 4.83 (1H, singlet); 6.27 (1H, singlet); 7.10–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 374 (M⁺ + 1), 304.

Elemental analysis: Calculated for C₂₀H₂₀FNO₃S: C, 64.32%; H, 5.40%; N, 3.75%; Found: C, 64.46%; H, 5.39%; N, 3.73%.

EXAMPLE 24

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 192)

Following a procedure similar to that described in Example 23, except that an equivalent amount of propionic anhydride was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 101°–102° C., in a yield of 16%.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹: 1705, 1760.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.75–0.90 (2H, multiplet); 0.90–1.10 (2H, multiplet); 1.21 (3H, triplet, J=6.7 Hz); 2.15–2.37 (1H, multiplet); 2.55 (2H, quartet, J=6.7 Hz); 2.65–2.95 (4H, multiplet); 3.40–3.60 (2H, multiplet); 4.80 (1H, singlet); 6.25 (1H, singlet); 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 388 (M⁺ + 1), 318.

Elemental analysis: Calculated for C₂₁H₂₂FNO₃S: C, 65.10%; H, 5.72%; N, 3.61%; Found: C, 64.80%; H, 5.72%; N, 3.61%.

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EXAMPLE 25

2-Butyryloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 194)

Following a procedure similar to that described in Example 23, except that an equivalent amount of butyric anhydride was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 84°–85° C., in a yield of 39%.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹: 1756, 1706.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.75–1.10 (7H, multiplet); 1.65–1.85 (2H, multiplet); 2.21–2.34 (1H, multiplet); 2.49 (2H, triplet, J=7.0 Hz); 2.70–3.00 (4H, multiplet); 3.52 (2H, broad triplet, J=16.0 Hz); 4.82 (1H, singlet); 6.25 (1H, singlet); 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 402 (M⁺ + 1), 332.

Elemental analysis: Calculated for C₂₂H₂₄FNO₃S: C, 65.81%; H, 6.03%; N, 3.49%. Found: C, 65.92%; H, 5.91%; N, 3.41%.

EXAMPLE 26

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 196)

Following a procedure similar to that described in Example 23, except that an equivalent amount of pivalic anhydride was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 91°–94° C., in a yield of 44%.

Infrared Absorption Spectrum (KBr) ν_{max} cm⁻¹: 1749, 1700.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.79–0.92 (2H, multiplet); 0.98–1.09 (2H, multiplet); 1.31 (9H, singlet); 2.23–2.36 (1H, multiplet); 2.70–2.95 (4H, multiplet); 3.47 (1H, doublet, J=14.5 Hz); 3.58 (1H, doublet, J=14.5 Hz); 4.83 (1H, singlet); 6.26 (1H, singlet); 7.05–7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 416 (M⁺ + 1), 346.

Elemental analysis: Calculated for C₂₃H₂₆FNO₃S: C, 66.48%; H, 6.31%; N, 3.37%; Found: C, 66.21%; H, 6.40%; N, 3.38%.

EXAMPLE 27

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-nonanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 199)

1.0 g (3.0 mmole) of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (prepared as described in Example 20) was dissolved in 15 ml of dimethylformamide, and then 0.18 g (4.5 mmole) of a 60% w/w dispersion of sodium hydride in mineral oil and 0.82 ml (4.5 mmole) of nonanoyl chloride were added, in that order, to the resulting mixture, whilst ice-cooling. The resulting reaction mixture was then stirred at the same temperature for 30 minutes, after which it was stirred at room temperature for a further 5 hours. 300 ml of ethyl acetate were then added to the mixture, which was then washed with a saturated aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order. The organic layer was separated and dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pres-

sure. The resulting residue was subjected to silica gel column chromatography, using a 100:2 by volume mixture of toluene and ethyl acetate as the eluent, to give a yellow oil. The oil was crystallized from petroleum ether to obtain the title compound as white crystals, melting at 45°-48° C., in a yield of 40%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.80-1.80 (19H, multiplet); 2.21-2.32 (1H, multiplet); 2.53 (2H, triplet, J=7.5 Hz); 2.70-2.95 (4H, multiplet); 3.48 (1H, doublet, J=15.0 Hz); 3.57 (1H, doublet, J=15.0 Hz); 4.84 (1H, singlet); 6.27 (1H, singlet); 7.05-7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 472 (M⁺+1), 402.

Elemental analysis: Calculated for C₂₇H₃₄FNO₃S: C, 68.76%; H, 7.27%; N, 2.97%. Found: C, 68.56%; H, 7.49%; N, 2.97%.

EXAMPLE 28

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-decanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 200)

28(a) Following a procedure similar to that described in Example 27, except that an equivalent amount of decanoyl chloride was used in place of the nonanoyl chloride, the title compound was obtained as a yellow oil in a yield of 40%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.80-1.80 (21H, multiplet); 2.18-2.32 (1H, multiplet); 2.52 (2H, triplet, J=7.5 Hz); 2.70-2.97 (4H, multiplet); 3.50 (1H, doublet, J=14.5 Hz); 3.59 (1H, doublet, J=14.5 Hz); 4.85 (1H, singlet); 6.26 (1H, singlet); 7.20-7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 486 (M⁺+1), 416.

28(b) A procedure similar to that described in Example 2(b) was repeated, using the title compound prepared as described in step (a) above, except that diisopropyl ether was used as a solvent in place of the diethyl ether, to give the hydrochloride of the title compound as yellow crystals, melting at 62°-64° C., in a yield of 81%.

Elemental analysis: Calculated for C₂₈H₃₆FNO₃S.HCl: C, 64.41%; H, 7.14%; N, 2.68%. Found: C, 64.12%; H, 7.05%; N, 2.63%.

EXAMPLE 29

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-palmitoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 201)

Following a procedure similar to that described in Example 27, except that an equivalent amount of palmitoyl chloride was used in place of the nonanoyl chloride, the title compound was obtained as white crystals, melting at 66.20-68° C., in a yield of 21%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.80-1.80 (33H, multiplet); 2.20-2.32 (1H, multiplet); 2.51 (2H, triplet, J=7.5 Hz); 2.70-2.95 (4H, multiplet); 3.48 (1H, doublet, J=15.0 Hz); 3.58 (1H, doublet, J=15.0 Hz); 4.84 (1H, singlet); 6.26 (1H, singlet); 7.10-7.55 (4H, multiplet).

Mass spectrum (CI, m/z): 570 (M⁺+1), 500.

Elemental analysis: Calculated for C₃₄H₄₈FNO₃S: C, 71.66%; H, 8.49%; N, 2.46%. Found: C, 71.72%; H, 8.62%; N, 2.43%.

EXAMPLE 30

2-t-Butoxycarbonyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 203)

Following a procedure similar to that described in Example 23, except that an equivalent amount of di-*t*-butyl dicarbonate was used in place of the acetic anhydride, the title compound was obtained as white crystals, melting at 98°-99° C., in a yield of 15%.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 0.80-0.90 (2H, multiplet); 0.98-1.09 (2H, multiplet); 1.55 (9H, singlet); 2.20-2.34 (1H, multiplet); 2.70-2.95 (4H, multiplet); 3.40-3.60 (2H, multiplet); 4.83 (1H, singlet); 6.27 (1H, singlet); 7.07-7.52 (4H, multiplet).

Mass spectrum (CI, m/z): 432 (M⁺+1), 362.

Elemental analysis: Calculated for C₂₃H₂₆FNO₄S: C, 64.02%; H, 6.07%; N, 3.25%. Found: C, 63.57%; H, 6.03%; N, 3.27%.

EXAMPLE 31

2-Amino-5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 177)

5 ml of hydrochloric acid were added to 0.4 g of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (prepared as described in Example 18), and then 0.23 g of tin powder was added to the resulting mixture, whilst stirring, after which the mixture was stirred at room temperature for a further hour. 10 ml of water were added to the reaction mixture, which was then extracted with methylene chloride. The methylene chloride layer was removed, and the aqueous layer was concentrated to dryness by evaporation under reduced pressure, and then crystallized from diethyl ether, to give a complex of the title compound with stannic chloride as a pale yellow powder in a yield of 72%.

Nuclear Magnetic Resonance Spectrum (CD₃OD) δ ppm: 0.95-1.05 (2H, multiplet); 1.20-1.35 (2H, multiplet); 1.85-1.99 (1H, multiplet); 3.60-3.80 (2H, multiplet); 6.07 (1H, singlet); 7.35-7.80 (4H, multiplet).

EXAMPLE 32

2-Acetyl-amino-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 179)

1.85 g (5.13 mmole) of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (prepared as described in Example 18) were dissolved in a mixture of 20 ml of acetic acid and 2 ml of acetic anhydride, and then 1.85 g of iron powder were added to the solution, whilst stirring at room temperature; the mixture was then stirred at the same temperature for 90 minutes. At the end of this time, water and chloroform were added to the reaction mixture, and the mixture was neutralized with sodium carbonate. The inorganic salt thus precipitated was filtered off, the remaining organic layer was separated and the aqueous layer was extracted with chloroform. The organic layer and the extract were combined and dried over anhydrous magnesium sulfate, and then the solvent was removed by distillation under reduced pressure. The resulting residue was then subjected to silica gel column chromatography, using a 6:4 by volume mixture of

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toluene and ethyl acetate as the eluent, to give 1.86 g of the title compound. This was crystallized from diisopropyl ether to obtain 1.37 g of the title compound as white crystals, melting at 155°–159° C.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.78–0.94 (2H, multiplet); 0.98–1.12 (2H, multiplet); 2.17 (3H, singlet); 2.15–2.32 (1H, multiplet); 2.70–2.99 (4H, multiplet); 3.50 (1H, doublet, $J=11.4$ Hz); 3.60 (1H, doublet, $J=11.4$ Hz); 4.86 (1H, singlet); 6.27 (1H, singlet); 7.10–7.55 (4H, multiplet); 7.80–8.00 (1H, broad singlet).

Mass spectrum (CI, m/z): 373 ($M^+ + 1$), 303.

Elemental analysis: Calculated for $\text{C}_{20}\text{H}_{21}\text{FN}_2\text{O}_2\text{S}$: C, 64.49%; H, 5.68%; N, 7.52%; Found: C, 64.38%; H, 5.50%; N, 7.38%.

EXAMPLE 33

2-Butyrylamino-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 181)

Following a procedure similar to that described in Example 32, except that equivalent amounts of butyric acid and butyric anhydride were used in place of the acetic acid and acetic anhydride, the title compound was obtained as white crystals, melting at 154°–157° C., in a yield of 61%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.78–0.94 (2H, multiplet); 0.90–1.10 (5H, multiplet); 1.65–1.82 (2H, multiplet); 2.21–2.39 (3H, multiplet); 2.69–2.95 (4H, multiplet); 3.47 (1H, doublet, $J=11.4$ Hz); 3.56 (1H, doublet, $J=11.4$ Hz); 4.81 (1H, singlet); 6.25 (1H, singlet); 7.10–7.60 (4H, multiplet); 7.70 (1H, singlet).

Mass spectrum (CI, m/z): 401 ($M^+ + 1$), 331.

Elemental analysis: Calculated for $\text{C}_{22}\text{H}_{25}\text{FN}_2\text{O}_2$: C, 65.97%; H, 6.29%; N, 6.99%; Found: C, 65.95%; H, 6.36%; N, 6.95%.

EXAMPLE 34

Optically active

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 59)

0.3 g of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (prepared as described in Example 12) was separated into fractions by liquid chromatography [column: DAICEL CHI-RALPAC AD (trade name), 1 cm $\times$ 25 cm; eluent: a 1000:40:1 by volume mixture of hexane, isopropanol and diethylamine; column temperature: 35° C.; flow rate: 4 ml/minute], to obtain an optically active isomer A [retention time: 8.3 minutes; specific rotation angle $[\alpha]_D^{25}$: 109.4° ($C=1.80$, CHCl_3)] and an isomer B [retention time: 9.9 minutes; specific rotation angle $[\alpha]_D^{25}$: 100.1° ($C=1.90$, CHCl_3)].

Isomers A and B were separately dissolved in diethyl ether, and then hydrogen chloride gas was allowed to act upon the resulting solutions to obtain 0.13 g and 0.12 g of the hydrochlorides of isomer A and isomer B, respectively, as white crystals.

Hydrochloride of isomer A

melting at 106°–110° C.

Elemental analysis: Calculated for $\text{C}_{18}\text{H}_{18}\text{FNOS} \cdot \text{HCl} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 59.17%; H, 5.65%; N, 3.83%; Found: C, 59.06%; H, 5.74%; N, 3.90%.

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Hydrochloride of isomer B

melting at 105°–110° C.

Elemental analysis: Calculated for $\text{C}_{18}\text{H}_{18}\text{FNOS} \cdot \text{HCl} \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 59.91%; H, 5.59%; N, 3.88%; Found: C, 59.80%; H, 5.84%; N, 3.79%.

EXAMPLE 35

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 207)

1.0 g (3.0 mmole) of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno [3,2-c]pyridine (prepared as described in Example 20) was dissolved in 20 ml of dimethylformamide, and then 100 mg (0.6 mmole) of potassium iodide and 0.13 g (3.3 mmole) of a 60% dispersion of sodium hydride in mineral oil were added to the solution at room temperature; the mixture was then stirred at the same temperature for 10 minutes. At the end of this time, a solution of 0.43 ml (3.0 mmole) of pivaloyloxymethyl chloride in 5 ml of dimethylformamide was added dropwise to the resulting mixture over a period of 10 minutes, and the resulting mixture was stirred at room temperature for 30 minutes. 300 ml of ethyl acetate were added to the reaction mixture, and the mixture was washed three times, each time with 50 ml of a saturated aqueous solution of sodium hydrogen carbonate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed by evaporation under reduced pressure. The resulting residue was subjected to silica gel column chromatography, using a 100:3 by volume mixture of toluene and ethyl acetate as the eluent, to give the title compound as a colorless oil in a yield of 15%.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1} : 1715, 1702.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.79–0.93 (2H, multiplet); 0.99–1.14 (2H, multiplet); 1.22 (9H, singlet); 2.18–2.31 (1H, multiplet); 2.65–2.95 (4H, multiplet); 3.44 (1H, doublet, $J=15.5$ Hz); 3.55 (1H, doublet, $J=15.5$ Hz); 4.84 (1H, singlet); 5.57 (2H, singlet); 6.04 (1H, singlet); 7.05–7.50 (4H, multiplet).

Mass spectrum (CI, m/z): 446 ($M^+ + 1$), 376.

EXAMPLE 36

5-(α -Cyclopropylcarbonyl-2-fluorobenzyl)-2-methoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and its hydrochloride (Compound No. 210)

36(a) A procedure similar to that described in Example 35 was repeated, except that an equivalent amount of methyl iodide was used in place of the pivaloyloxymethyl chloride and potassium iodide, to give the title compound as a yellow oil in a yield of 45%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 0.80–0.92 (2H, multiplet); 1.00–1.10 (2H, multiplet); 2.20–2.36 (1H, multiplet); 2.65–2.96 (4H, multiplet); 3.42 (1H, doublet, $J=14.5$ Hz); 3.55 (1H, doublet, $J=14.5$ Hz); 3.80 (3H, singlet); 4.82 (1H, singlet); 5.80 (1H, singlet);

7.10–7.60 (4H, multiplet).

Mass spectrum (CI, m/z): 346 ($M^+ + 1$), 276.

36(b) Following a procedure similar to that described in Example 2(b), using the whole of the title compound prepared as described in step (a) above, the hydrochloride of the title compound was obtained as white crystals, melting at 102°–106° C., in a yield of 78%.

Elemental analysis:

Calculated for $C_{19}H_{20}FNO_2 \cdot S \cdot HCl \cdot \frac{1}{2}H_2O$: C, 58.38%; H, 5.67%; N, 3.58%; Found: C, 58.08%; H, 5.77%; N, 3.53%.

EXAMPLE 37

5-[α -(2-Fluorocyclopropylcarbonyl)-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 275)

Following a procedure similar to that described in Example 1, except that equivalent amounts of 2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine hydrochloride and 2-fluoro- α -(2-fluorocyclopropylcarbonyl)-benzyl bromide (prepared as described in Preparation 27) were used in place of the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and 2-chloro- α -tri-fluoroacetylbenzyl bromide, the title compound was obtained as a yellow oil in a yield of 31%.

The resulting 5-[α -(2-fluorocyclopropylcarbonyl)-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine (Compound No. 275) is believed to contain a small quantity of the tautomeric 5-[α -(2-fluorocyclopropylcarbonyl)-2-fluorobenzyl]-2-hydroxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (Compound No. 274), from which it was not separated.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1} : 1680.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.48–1.55 (2H, multiplet); 1.85–2.01 (1H, multiplet); 2.30–2.51 (2H, multiplet); 2.53–2.90 (1H, multiplet); 3.00–3.20 (2H, multiplet); 3.83–4.01 & 4.03–4.18 (together 2H, each multiplet); 4.46–4.60 & 4.79–4.92 (together 2H, each multiplet); 6.05 & 6.09 (together 1H, each singlet); 7.10–7.45 (4H, multiplet). Mass spectrum (CI, m/z): 350 ($M+1$), 262.

PREPARATION 1

3-(2-Chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine

A solution of 5.0 g (29.3 mmole) of o-chlorophenylacetic acid and 0.3 g of p-toluenesulfonic acid monohydrate in 50 ml of methanol was heated under reflux for 6 hours. At the end of this time, 3.1 g (44 mmole) of hydroxylamine hydrochloride were added to the reaction mixture, followed by 2.1 g of sodium methoxide. The resulting reaction mixture was then heated under reflux for 10 hours. 14.2 g (103 mmole) of potassium carbonate and 5.1 ml of 1,2-dibromoethane were then added to the resulting reaction mixture, followed by 15 ml of water. The reaction mixture was then heated under reflux for a further 10 hours. At the end of this time, 200 ml of ethyl acetate were added to the reaction mixture, and the organic layer was separated, washed with a saturated aqueous solution of sodium hydrogen-carbonate and dried over anhydrous sodium sulfate; the solvent was then removed by distillation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 9:1 by volume mixture of toluene and ethyl acetate as the eluent, to give 4.9 g of the title compound as an oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.67 (2H, singlet); 4.05 (2H, triplet, $J=4.2$ Hz); 4.29 (2H, triplet, $J=4.2$ Hz); 7.10–7.40 (4H, multiplet). Mass spectrum (CI, m/z): 212 ($M+1$), 176.

PREPARATION 2

3-(2-Fluorobenzyl)-5,6-dihydro-1,4,2-dioxazine

A procedure similar to that described in Preparation 1 was repeated, except that an equivalent amount of o-fluorophenylacetic acid was used in place of the o-chlorophenylacetic acid, to give the title compound as a colorless oil in a yield of 45%.

Mass spectrum (CI, m/z): 196 ($M+1$), 109.

PREPARATION 3

3-(2,6-Difluorobenzyl)-5,6-dihydro-1,4,2-dioxazine

A procedure similar to that described in Preparation 1 was repeated, except that an equivalent amount of 2,6-difluorophenylacetic acid was used in place of the o-chlorophenylacetic acid, to give the title compound as a colorless oil in a yield of 45%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.61 (2H, singlet); 4.04 (2H, triplet, $J=4.1$ Hz); 4.30 (2H, triplet, $J=4.1$ Hz); 6.80–7.30 (4H, multiplet).

Mass spectrum (CI, m/z): 214 ($M+1$), 127.

PREPARATION 4

2-Chlorobenzyl cyclopropyl ketone

10 ml of anhydrous diethyl ether were added to 0.45 g (18.5 mmole) of metallic magnesium, and then a solution of 2.0 ml (15.4 mmole) of 2-chlorobenzyl bromide in 10 ml of diethyl ether was slowly added dropwise to the resulting mixture, whilst stirring; the mixture was then stirred at room temperature for one hour. The resulting solution was slowly added dropwise to a solution of 1.1 ml of cyclopropyl cyanide in 10 ml of diethyl ether over a period of 30 minutes, and then the mixture was stirred at room temperature for 2 hours. At the end of this time, a saturated aqueous solution of ammonium chloride was added to the reaction mixture, and the mixture was stirred at room temperature for 15 minutes. 200 ml of ethyl acetate were then added to the reaction mixture, and the organic layer was separated, washed with water, with a saturated aqueous solution of sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, in that order, and dried over anhydrous sodium sulfate; the solvent was then removed by distillation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 9:1 by volume mixture of toluene and ethyl acetate as the eluent, to give 2.0 g of the title compound as a colorless oil.

Infrared Absorption Spectrum (thin film) ν_{max} cm^{-1} : 1695.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.86–0.92 (2H, multiplet); 1.06–1.12 (2H, multiplet); 1.96–2.02 (1H, multiplet); 3.98 (2H, singlet); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z): 195 ($M+1$), 159.

PREPARATION 5

1-(2-Fluorophenyl)-2-pentanone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and butyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 36%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, $J=8.0$ Hz); 1.52–1.73 (2H, multi-

plet); 2.45 (2H, triplet, $J=8.0$ Hz); 3.70 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z): 181 ($M+1$), 109.

PREPARATION 6

1-(2-Fluorophenyl)-2-hexanone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and pentyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 46%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, $J=8.0$ Hz); 1.20–1.39 (2H, multiplet); 1.50–1.65 (2H, multiplet); 2.50 (2H, triplet, $J=8.0$ Hz); 3.70 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z): 195 ($M+1$), 109.

PREPARATION 7

1-(2-Fluorophenyl)-3,3-dimethyl-2-butanone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and *t*-butyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 42%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.25 (9H, singlet); 3.80 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z): 195 ($M+1$), 109.

PREPARATION 8

Cyclopropyl 2-fluorobenzyl ketone

A procedure similar to that described in Preparation 4 was repeated, except that equivalent amounts of 2-fluorobenzyl bromide and cyclopropyl cyanide were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, to give the title compound as a colorless oil in a yield of 70%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.82–0.98 (2H, multiplet); 1.03–1.17 (2H, multiplet); 1.92–2.06 (1H, multiplet); 3.86 (2H, singlet); 7.10–7.30 (4H, multiplet).

Mass spectrum (CI, m/z): 179 ($M+1$).

PREPARATION 9

1-(2-Fluorophenyl)-2-butanone

(a) 1-(2-Fluorophenyl)-2-nitro-1-butene 30 ml of acetic acid were added to 4.73 g (38.11 mmole) of 2-fluorobenzaldehyde, 4.41 g (49.49 mmole) of nitropropane and 3.23 g (41.90 mmole) of ammonium acetate, and the resulting mixture was heated under reflux, whilst stirring, for 4 hours. At the end of this time, the reaction mixture was cooled to room temperature, neutralized with an aqueous solution of sodium hydrogen-carbonate and extracted with diethyl ether. The extract was dried over anhydrous magnesium sulfate, and then xylene was added to the solution. The mixture was concentrated by evaporation under reduced pressure, to give 7.4 g of the title compound as a pale yellow oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.25 (3H, triplet, $J=6.5$ Hz); 2.80 (2H, quartet, $J=6.5$ Hz); 7.00–7.60 (4H, multiplet); 8.03 (1H, singlet).

Mass spectrum (CI, m/z): 196 ($M+1$), 149.

9(b) 1-(2-Fluorophenyl)-2-butanone

100 ml of 90% v/v aqueous acetic acid were added to 7.4 g of 1-(2-fluorophenyl)-2-nitro-1-butene [prepared

as described in step (a) above], and then 12.11 g (190 mmole) of a zinc powder were added in portions to the resulting solution, whilst heating. The mixture was then heated under reflux, whilst stirring, for 4 hours. At the end of this time, the reaction mixture was left to stand overnight, and then the crystals which had precipitated were filtered off and washed with toluene. The filtrate was combined with the toluene washings, and the mixture was concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using toluene as the eluent, to give 1.85 g of the title compound as a pale brown oil.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.05 (3H, triplet, $J=7.0$ Hz); 2.53 (2H, quartet, $J=7.0$ Hz); 3.73 (2H, singlet); 7.00–7.40 (4H, multiplet).

Mass spectrum (CI, m/z): 167 ($M+1$), 109.

PREPARATION 10

1-(2-Chlorophenyl)-2-propanone

Following a procedure similar to that described in Preparation 9, except that equivalent amounts of 2-chlorobenzaldehyde and nitroethane were used in place of the 2-fluorobenzaldehyde and nitropropane, the title compound was obtained as a brown oil in a yield of 27%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.20 (3H, singlet); 3.85 (2H, singlet); 7.15–7.45 (4H, multiplet).

Mass spectrum (CI, m/z): 169 ($M+1$), 125.

PREPARATION 11

1-(2-chlorophenyl)-2-butanone

Following a procedure similar to that described in Preparation 9, except that an equivalent amount of 2-chlorobenzaldehyde was used in place of the 2-fluorobenzaldehyde, the title compound was obtained as a pale yellow oil in a yield of 17%.

Mass spectrum (CI, m/z): 183 ($M+1$), 125.

PREPARATION 12

1-(2-Chlorophenyl)-2-heptanone

Following a procedure similar to that described in Preparation 9, except that equivalent amounts of 2-chlorobenzaldehyde and nitrohexane were used in place of the 2-fluorobenzaldehyde and nitropropane, the title compound was obtained as a pale yellow oil in a yield of 17%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.90 (3H, triplet, $J=8.0$ Hz); 1.20–1.40 (4H, multiplet); 1.50–1.70 (2H, multiplet); 2.50 (2H, triplet, $J=10.0$ Hz); 3.80 (2H, singlet); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z): 225 ($M+1$), 125.

PREPARATION 13

Cyclobutyl 2-fluorobenzyl ketone

20 ml of anhydrous diethyl ether were added to 1.06 g (44 mmole) of metallic magnesium, and then a solution of 7.56 g (40 mmole) of 2-fluorobenzyl bromide in 10 ml of diethyl ether was slowly added dropwise to the resulting mixture, whilst stirring; the mixture was then stirred at room temperature for 1 hour. The resulting solution was slowly added dropwise to a solution of 4.74 g (40 mmole) of cyclobutanecarbonyl chloride in

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30 ml of tetrahydrofuran, whilst cooling in a methanol-dry ice bath, over a period of 2 hours, and then the mixture was allowed to return to room temperature, whilst stirring, over a period of 2 hours. At the end of this time, 100 ml of water and 150 ml of diethyl ether were added to the reaction mixture, and the organic layer was separated, dried over anhydrous magnesium sulfate and concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 9:1 by volume mixture of toluene and hexane as the eluent, to give 2.97 g of the title compound as a pale yellow oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 1.65–2.40 (6H, multiplet); 3.31–3.48 (1H, multiplet); 3.67 (2H, singlet); 7.00–7.30 (4H, multiplet).

Mass spectrum (CI, m/z): 193 ($M^+ + 1$), 137.

PREPARATION 14

5-Chloro-1-(2-chlorophenyl)-2-pentanone

Following a procedure similar to that described in Preparation 13, except that equivalent amounts of 2-chlorobenzyl bromide and 4-chlorobutyl chloride were used in place of the 2-fluorobenzyl bromide and cyclobutanecarbonyl chloride, the title compound was obtained as a yellow oil in a yield of 79%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 1.96–2.15 (2H, multiplet); 2.69 (2H, triplet, $J=7.7$ Hz); 3.56 (2H, triplet, $J=7.7$ Hz); 3.86 (2H, singlet); 7.10–7.50 (4H, multiplet).

PREPARATION 15

1-(2-Chlorophenyl)-3,3,3-trifluoro-2-propanone

10 ml of anhydrous diethyl ether were added to 0.9 g (37.0 mmole) of metallic magnesium, and then a solution of 3.9 ml (30.8 mmole) of 2-chlorobenzyl chloride in 10 ml of diethyl ether was slowly added dropwise to the resulting mixture, with vigorous stirring, over a period of 30 minutes; the mixture was then stirred at room temperature for 1 hour. The resulting solution was slowly added dropwise to a solution of 4.3 ml (30.8 mmole) of trifluoroacetic anhydride in 40 ml of tetrahydrofuran, whilst cooling to about -70°C ., and then the mixture was allowed to return to room temperature, whilst stirring, over a period of about 1 hour; after this, the mixture was left to stand overnight. At the end of this time, 200 ml of ethyl acetate were added to the resulting reaction mixture, and the organic layer was separated, washed with 1N aqueous hydrochloric acid and with a saturated aqueous solution of sodium chloride, in that order, dried over anhydrous sodium sulfate and concentrated by evaporation under reduced pressure. The residue thus obtained was subjected to silica gel column chromatography, using a 10:2 by volume mixture of toluene and ethyl acetate as the eluent, to give 5.7 g of the title compound as a yellow oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 4.16 (2H, singlet); 7.10–7.50 (4H, multiplet).

Mass spectrum (CI, m/z): 223 ($M^+ + 1$), 125.

PREPARATION 16

2-Chloro- α -trifluoroacetylbenzyl bromide

2.0 g (9.0 mmole) of 1-(2-chlorophenyl)-3,3,3-trifluoro-2-propanone were dissolved in 30 ml of carbon tetrachloride, and then 0.46 ml (9.0 mmole) of bromine was added to the solution, which was then stirred at room temperature for 10 hours. At the end of this time, sodium hydrosulfite was added to the reaction mixture,

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and the mixture was stirred at room temperature for 15 minutes, after which insolubles were removed by filtration. The filtrate was concentrated by evaporation under reduced pressure, and the residue was subjected to silica gel column chromatography, using a 10:2 by volume mixture of toluene and ethyl acetate as the eluent, to give 0.87 g of the title compound as a yellow oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 6.39 (1H, singlet); 7.30–7.70 (4H, multiplet).

Mass spectrum (CI, m/z): 302 ($M^+ + 2$), 300 (M^+), 221.

PREPARATION 17

2-Chloro- α -(4-chlorobutyl)benzyl bromide

Following a procedure similar to that described in Preparation 16, except that an equivalent amount of 1-(2-chlorophenyl)-5-chloro-2-pentanone was used in place of the 1-(2-chlorophenyl)-3,3,3-trifluoro-2-propanone, the title compound was obtained as a yellow oil in a yield of 72%.

Nuclear Magnetic Resonance Spectrum (CDCl_3) δ ppm: 2.01–2.14 (2H, multiplet); 2.40–2.90 (2H, multiplet); 3.49–3.61 (2H, multiplet); 5.98 (1H, singlet); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z): 311 ($M^+ + 1$), 231.

PREPARATION 18

2-Chloro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide

4.0 g (19 mmole) of 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine (prepared as described in Preparation 1) were dissolved in 40 ml of carbon tetrachloride, and then 4.1 g (23 mmole) of N-bromosuccinimide and 0.2 g of benzoyl peroxide were added to the solution, which was then stirred, whilst heating, for 8 hours. At the end of this time, 100 ml of ethyl acetate and 100 ml of hexane were added to the solution, and the mixture was stirred at room temperature for 30 minutes; insolubles were then removed by filtration. The filtrate was concentrated by evaporation under reduced pressure, to give 4.8 g of the title compound as a yellow oil.

Mass spectrum (CI, m/z): 292 ($M^+ + 3$), 290 ($M^+ + 1$), 212.

PREPARATION 19

2-Fluoro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide

Following a procedure similar to that described in Preparation 18, except that an equivalent amount of 3-(2-fluorobenzyl)-5,6-dihydro-1,4,2-dioxazine (prepared as described in Preparation 2) was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, the title compound was obtained as a red oil in a yield of 98%.

Mass spectrum (CI, m/z): 276 ($M^+ + 3$), 194.

PREPARATION 20

2,6-Difluoro- α -(5,6-dihydro-1,4,2-dioxazin-3-yl)benzyl bromide

Following a procedure similar to that described in Preparation 18, except that an equivalent amount of 3-(2,6-difluorobenzyl)-5,6-dihydro-1,4,2-dioxazine (prepared as described in Preparation 3) was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, the title compound was obtained as a red oil in a yield of 57%.

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Mass spectrum (CI, m/z) : 294 ($M^+ + 3$), 214.

PREPARATION 21

2-Chloro- α -cyclopropylcarbonylbenzyl bromide

Following a procedure similar to that described in Preparation 18, except that an equivalent amount of 2-chlorobenzyl cyclopropyl ketone (prepared as described in Preparation 4) was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, the title compound was obtained as a red oil in a yield of 83%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 0.80–1.20 (4H, multiplet); 2.04–2.16 (1H, multiplet); 6.18 (1H, singlet); 7.20–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 275 ($M^+ + 3$), 193.

PREPARATION 22

2-Chlorobenzyl 4-fluorophenyl ketone

Following a procedure similar to that described in Preparation 13, except that equivalent amounts of 2-chlorobenzyl bromide and 4-fluorobenzoyl chloride were used in place of the 2-fluorobenzyl bromide and cyclobutanecarbonyl chloride, the title compound was obtained as a colorless powder in a yield of 34%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 4.40 (2H, singlet); 7.10–7.45 (6H, multiplet); 8.04–8.10 (2H, multiplet).

Mass spectrum (CI, m/z) : 249 ($M^+ + 1$), 213.

PREPARATION 23

2-Fluorobenzyl isopropyl ketone

Following a procedure similar to that described in Preparation 4, except that equivalent amounts of 2-fluorobenzyl chloride and isobutyronitrile were used in place of the 2-chlorobenzyl bromide and cyclopropyl cyanide, the title compound was obtained as a colorless oil in a yield of 25%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 1.15 (6H, doublet, $J=7.5$ Hz); 2.75 (1H, septet, $J=7.5$ Hz); 3.78 (2H, singlet); 6.97–7.30 (4H, multiplet).

Mass spectrum (CI, m/z) : 181 ($M^+ + 1$), 109.

PREPARATION 24

2-Nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

24(a) 5-Acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

35.1 g (200 mmole) of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride and 38.57 g (200 mmole) of 28% w/v sodium methoxide in methanol were added to 200 ml of ethanol, and the resulting mixture was stirred at room temperature for 1 hour. The inorganic salt thus precipitated was filtered off, and the filtrate was concentrated to dryness by evaporation under reduced pressure. 50 ml of acetic anhydride were added all at once, whilst stirring, to the residue, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was then concentrated to dryness by evaporation under reduced pressure, and the residue thus obtained was subjected to silica gel column chromatography, using a 6:4 by volume mixture of toluene and ethyl acetate as the eluent, to give 29.32 g of the title compound as a yellow oil.

24(b) 5-Acetyl-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

20 ml of an acetic anhydride solution containing 5.43 g (30 mmole) of 5-acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine [prepared as described in step (a) above]

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were added dropwise at 10° to 18° C. over a period of one hour to 30 ml of an acetic acid solution containing 4.2 g (60 mmole) of 90% fuming nitric acid, and the mixture was then stirred at a temperature not greater than 18° C. for 1 hour. The reaction mixture was then poured into ice-water and extracted with methylene chloride. The organic layer was separated, washed with a saturated aqueous solution of sodium hydrogencarbonate and with water, in that order, and dried over anhydrous magnesium sulfate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was crystallized from a mixture of hexane and toluene, to give 4.46 g of the title compound as yellow crystals.

15 Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 2.19 & 2.21 (together 3H, each singlet); 2.82–3.05 (2H, multiplet); 3.80 & 3.95 (together 2H, each triplet, $J=5.7$ Hz); 4.55 & 4.66 (together 2H, each singlet); 7.66 (1H, singlet).

20 Mass spectrum (CI, m/z) : 227 ($M^+ + 1$).

24(c) 2-Nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride 2.38 g (10.53 mmole) of 5-acetyl-2-nitro-4,5,6,7-tetrahydrothieno[3,2-c]pyridine [prepared as described in step (b) above] were heated under reflux for 2 hours in 60 ml of 10% w/v aqueous hydrochloric acid. The reaction mixture was then concentrated to dryness by evaporation under reduced pressure, to give 2.19 g of the title compound as brown crystals.

30 Nuclear Magnetic Resonance Spectrum (CD_3OD) δ ppm: 3.22 (2H, triplet, $J=6.2$ Hz); 3.60 (2H, triplet, $J=6.2$ Hz); 4.31 (2H, singlet); 7.87 (1H, singlet).

Mass spectrum (CI, m/z) : 185 ($M^+ + 1$).

PREPARATION 25

4,5,6,7-Tetrahydrofuro[3,2-c]pyridine

3.7 g (46 mmole) of a 37% aqueous formaldehyde solution were added dropwise at room temperature to 5.1 g (46 mmole) of 2-furylethylamine [the compound described, for example, in Brit., J. Pharmacol., 9, 376 (1954)], and the resulting mixture was stirred for about 15 minutes, after which it was extracted with diethyl ether. The organic extract was washed with water and dried over anhydrous sodium sulfate, and then the diethyl ether was removed by distillation under reduced pressure. 5 ml of dimethylformamide were added to the residue, and the resulting solution was added dropwise to 15 ml of dimethylformamide containing 3.6 g (100 mmole) of dry hydrogen chloride at room temperature. The resulting mixture was then stirred for 3 hours. At the end of this time, the greater part of the dimethylformamide was removed by distillation under reduced pressure, and then water and a 0.1N aqueous solution of sodium hydroxide were added to the residue so as to adjust its pH to a value of about 11; the mixture was then extracted with chloroform. The organic extract was washed with water and dried over anhydrous sodium sulfate. The chloroform was then removed by evaporation under reduced pressure, and the resulting residue was purified by silica gel column chromatography, using a 50:1 by volume mixture of chloroform and methanol as the eluent, to give the title compound as a brown oil in a yield of 27%.

65 Nuclear Magnetic Resonance Spectrum ($CDCl_3$) δ ppm: 3.10–3.20 (4H, multiplet); 3.70–3.80 (2H, multiplet); 6.20 (1H, singlet); 7.27 (1H, singlet).

Mass spectrum (CI, m/z) : 124 ($M^+ + 1$).

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PREPARATION 26

2-Fluorobenzyl 2-fluorocyclopropyl ketone

A procedure similar to that described in Preparation 18 was repeated, except that an equivalent amount of 2-fluorocyclopropylcarbonyl chloride was used in place of the cyclobutylcarbonyl chloride, to give the title compound as a colorless oil in a yield of 27 %.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 1.38–1.58 (2H, multiplet); 2.34–2.56 (1H, multiplet); 3.90 (2H, singlet); 4.54–4.61 & 4.86–4.93 (together 1H, each multiplet); 7.05–7.35 (4H, multiplet).

Mass spectrum (CI, m/z) : 197 (M⁺ + 1), 109.

PREPARATION 27

2-Fluoro- α -(2-fluorocyclopropylcarbonyl)benzyl bromide

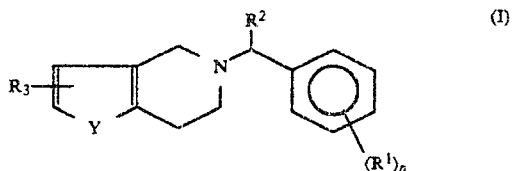
A procedure similar to that described in Preparation 18 was repeated, except that an equivalent amount of 2-fluorobenzyl 2-fluorocyclopropyl ketone was used in place of the 3-(2-chlorobenzyl)-5,6-dihydro-1,4,2-dioxazine, to give the title compound as a colorless oil in a yield of 76 %.

Nuclear Magnetic Resonance Spectrum (CDCl₃) δ ppm: 1.44–1.73 (2H, multiplet); 2.54–2.76 (1H, multiplet); 4.54–4.68 & 4.85–4.99 (together 1H, each multiplet); 5.93 (1H, singlet); 7.05–7.60 (4H, multiplet).

Mass spectrum (CI, m/z) : 277 (M⁺ + 2), 275 (M⁺), 195.

We claim:

1. A compound of formula (I):



wherein

R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a haloalkyl group having from 1 to 4 carbon atoms and at least one halogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a haloalkoxy group having from 1 to 4 carbon atoms and at least one halogen atom, an alkylthio group having from 1 to 4 carbon atoms, a haloalkylthio group having from 1 to 4 carbon atoms and at least one halogen atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a haloalkanoyl group having from 2 to 5 carbon atoms and at least one halogen atom, a carboxy group, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a haloalkanesulfonyl group having from 1 to 4 carbon atoms and at least one halogen atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 1 to 10 carbon atoms; a substituted alkanoyl group which has from 2 to 10 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; an alkenoyl group having from 3 to 6 carbon atoms; a substituted alkenoyl group which has from 3 to 6 carbon atoms and which is substituted by at

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least one substituent selected from the group consisting of substituents A, defined below; a cycloalkylcarbonyl group having from 4 to 8 carbon atoms; a substituted cycloalkylcarbonyl group which has from 4 to 8 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A, defined below; or a substituted benzoyl group having at least one substituent selected from the group consisting of substituents B, defined below;

R³ represents a hydrogen atom; a hydroxy group; an alkoxy group having from 1 to 4 carbon atoms; a substituted alkoxy group which has from 1 to 4 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents C, defined below; an aralkyloxy group in which the aralkyl part is as defined below; an alkanoyloxy group having from 1 to 18 carbon atoms; an alkenoyloxy group having from 3 to 6 carbon atoms; a cycloalkylcarbonyloxy group having from 4 to 8 carbon atoms; an arylcarbonyloxy group in which the aryl part is as defined below; an alkoxycarbonyloxy group having from 2 to 5 carbon atoms; an aralkyloxycarbonyloxy group in which the aralkyl part is as defined below; a phthalidylloxy group; a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group; a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group; a group of formula —N—R^aR^b; wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, alkyl groups having from 1 to 4 carbon atoms and substituted alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one substituent selected from the group consisting of substituents C, defined below; an aralkylamino group in which the aralkyl part is as defined below; an alkanoylamino group having from 1 to 18 carbon atoms; an alkenoylamino group having from 3 to 6 carbon atoms; a cycloalkylcarbonylamino group having from 4 to 8 carbon atoms; an arylcarbonylamino group in which the aryl part is as defined below; an alkoxycarbonylamino group having from 2 to 5 carbon atoms; an aralkyloxycarbonylamino group in which the aralkyl part is as defined below; a phthalidylamino group; a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylamino group; a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methylamino group, or a nitro group;

Y is a sulfur atom; and

n is an integer from 1 to 5, and, when n is an integer from 2 to 5, the groups represented by R¹ may be the same as or different from each other;

said substituents A are selected from the group consisting of halogen atoms, hydroxy groups, alkoxy groups having from 1 to 4 carbon atoms and cyano groups;

said substituents B are selected from the group consisting of alkyl groups having from 1 to 4 carbon atoms, halogen atoms and alkoxy groups having from 1 to 4 carbon atoms;

said substituents C are selected from the group consisting of alkoxy groups having from 1 to 4 carbon atoms, alkanoyloxy groups having from 1 to 6 carbon atoms and arylcarbonyloxy groups in which the aryl part is as defined below;

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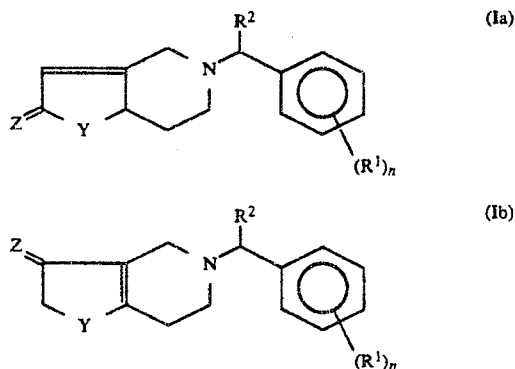
said aralkyl parts of said aralkyloxy, aralkyloxycarbonyloxy, aralkylamino and aralkyloxycarbonylamino groups are alkyl groups which have from 1 to 4 carbon atoms and which are substituted by at least one aryl groups as defined below; 5

said aryl groups and said aryl parts of said arylcarbonyloxy groups and of said arylcarbonylamino groups having from 6 to 10 carbon atoms in a carbocyclic ring which is unsubstituted or is substituted by at least one substituent selected from the 10 group consisting of substituents D, defined below; and

said substituents D are selected from the group consisting of the groups and atoms defined above in relation to R¹, other than said hydrogen atom; 15

or a tautomer thereof, or a pharmaceutically acceptable salt of said compound of formula (I) and of said tautomer.

2. The compound of claim 1, wherein said tautomer has the formula (Ia) or (Ib): 20



wherein R¹, R², Y and n are as defined above and Z represents group of formula =NH or an oxygen atom. 40

3. The compound of claim 1, wherein R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 45 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl 50 group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 1 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having 55 from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group.

4. The compound of claim 1, wherein R² represents an alkanoyl group having from 2 to 6 carbon atoms, a 60 substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms 65 and which is substituted by at least one substituent selected from the group consisting of substituents A',

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defined below of a substituted benzoyl group having at least one fluorine substituent; and

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups.

5. The compound of claim 1, wherein:

R³ represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyl group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula —NR^aR^b wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

6. The compound of claim 1, wherein:

R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an

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alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below or a substituted benzoyl group having at least one fluorine substituent;

R³ represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula —NR^aR^b wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl groups and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

7. The compound of claim 6, wherein n is from 1 to 3.

8. The compound of claim 6, wherein n is 1.

9. The compound of claim 1, wherein R¹ represents a hydrogen atom, a methyl group, an ethyl group, a halo-

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gen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group.

10. The compound of claim 1, wherein R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom.

11. The compound of claim 1, wherein R³ represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

12. The compound of claim 1, wherein:

R¹ represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)me-

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thoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

13. The compound of claim 12, wherein n is from 1 to 3.

14. The compound of claim 12, wherein n is 1.

15. The compound of claim 1, wherein R¹ represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group.

16. The compound of claim 1, wherein R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

17. The compound of claim 1, wherein:

R¹ represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

18. The compound of claim 17, wherein n is from 1 to 3.

19. The compound of claim 17, wherein n is 1.

20. The compound of claim 1, wherein R² represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom.

21. The compound of claim 1, wherein R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

22. The compound of claim 1, wherein:

R¹ represents a fluorine or chlorine atom;

R² represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

23. The compound of claim 22, wherein n is from 1 to 3.

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24. The compound of claim 22, wherein n is 1.

25. The compound of claim 1, selected from the group consisting of 5-(2-fluoro- α -propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

26. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

27. The compound of claim 1, selected from the group consisting of 5-(2-chloro- α -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

28. The compound of claim 1, selected from the group consisting of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

29. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

30. The compound of claim 1, selected from the group consisting of 2-butyryloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

31. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

32. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

33. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

34. The compound of claim 1, selected from the group consisting of 2-t-butoxycarbonyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

35. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

36. The compound of claim 1, selected from the group consisting of 5-(2-chloro- α -cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

37. The compound of claim 1, selected from the group consisting of 5-(2-fluoro- α -propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

38. The compound of claim 1, selected from the group consisting of 5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

39. The compound of claim 1, selected from the group consisting of 2-acetoxy-5-(2-chloro- α -cyclo-

propylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

40. The compound of claim 1, selected from the group consisting of 5-[α -(2-fluorocyclopropylcarbonyl)-2-fluorobenzyl]-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer and pharmaceutically acceptable salts thereof.

41. The compound of claim 1, selected from the group consisting of 2-acetoxy-5-[α -(2-fluorocyclopropylcarbonyl)-2-fluorobenzyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and pharmaceutically acceptable salts thereof.

42. A pharmaceutical composition for the treatment and prophylaxis of thrombosis or embolisms, comprising an effective amount of a blood platelet aggregation inhibitor in admixture with a pharmaceutically acceptable carrier or diluent, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof, as claimed in claim 1.

43. The composition of claim 42, wherein:

R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxy carbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, or a substituted benzoyl group having at least one fluorine substituent, or a;

R³ represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxy methoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkenoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxy carbonyloxy group having from 2

to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidylloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $-\text{NR}^a\text{R}^b$ wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl groups and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxy carbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

44. The composition of claim 42, wherein:

R¹ represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxy carbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzoyloxy group, an alkoxy carbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidylloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-

yl)methoxy group, an amino group or a t-butoxycarbonylamino group,

Y represents an oxygen or sulfur atom.

45. The composition of claim 42, wherein:

R¹ represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group;

46. The composition of claim 42, wherein:

R¹ represents a fluorine or chlorine atom;

R² represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms.

47. The composition of claim 42, wherein said blood platelet aggregation inhibitor is selected from the group consisting of:

5-(2-fluoro- α -propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro- α -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-butyryloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-t-butoxycarbonyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro- α -cyclopropylcarbonylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

5-(2-fluoro- α -propionylbenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

2-acetoxy-5-(2-chloro- α -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5[α -(2-fluorocyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its tautomer;

2-acetoxy-5-[α -(2-fluorocyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

and pharmaceutically acceptable salts thereof.

48. A method for the treatment or prophylaxis of thrombosis or embolisms, comprising administering to a mammal an effective amount of a blood platelet aggregation inhibitor, wherein said inhibitor is at least one compound of formula (I), or a tautomer or pharmaceutically acceptable salt thereof, as claimed in claim 1.

49. The method of claim 48, wherein:

R¹ represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, a halogen atom, a fluoroalkyl group having from 1 to 4 carbon atoms and at least one fluorine atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, a fluoroalkoxy group having from 1 to 4 carbon atoms and at least one fluorine atom, an alkylthio group having from 1 to 4 carbon atoms, a fluoroalkylthio group having from 1 to 4 carbon atoms and at least one fluorine atom, an amino group, an alkanoyl group having from 1 to 5 carbon atoms, a fluoroalkanoyl group having from 2 to 5 carbon atoms and at least one fluorine atom, an alkoxycarbonyl group having from 2 to 5 carbon atoms, a carbamoyl group, a cyano group, a nitro group, an alkanesulfonyl group having from 1 to 4 carbon atoms, a fluoroalkanesulfonyl group having from 1 to 4 carbon atoms and at least one fluorine atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, a substituted cycloalkylcarbonyl group which has from 4 to 7 carbon atoms and which is substituted by at least one substituent selected from the group consisting of substituents A', defined below, of a substituted benzoyl group having at least one fluorine substituent;

R³ represents a hydrogen atom, a hydroxy group, an alkoxy group having from 1 to 4 carbon atoms, an alkoxymethoxy group in which the alkoxy part has from 1 to 4 carbon atoms, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkanoyloxy group having from 1 to 18 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 4 to 7 carbon atoms, a benzyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonyloxy group having from 2

to 5 carbon atoms, a benzyloxycarbonyloxy group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a group of formula $-NR^aR^b$ wherein R^a and R^b are independently selected from the group consisting of hydrogen atoms, methyl groups and ethyl groups or R^a represents a hydrogen atom and R^b represents an alkanoyloxymethyl group in which the alkanoyl part has from 1 to 5 carbon atoms,

a benzylamino group, an alkanoylamino group having from 1 to 18 carbon atoms, an alkenoylamino group having 3 or 4 carbon atoms, a cycloalkylcarbonylamino group having 6 or 7 carbon atoms, a benzoylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below, an alkoxycarbonylamino group having from 2 to 5 carbon atoms or a benzyloxycarbonylamino group which is unsubstituted or is substituted by at least one substituent selected from the group consisting of substituents D', defined below;

said substituents A' are selected from the group consisting of fluorine atoms, chlorine atoms, hydroxy groups, methoxy groups, ethoxy groups and cyano groups; and

said substituents D' are selected from the group consisting of fluorine atoms, chlorine atoms, methyl groups and methoxy groups.

50. The method of claim 48, wherein:

R¹ represents a hydrogen atom, a methyl group, an ethyl group, a halogen atom, a methyl group substituted by at least one fluorine atom, a hydroxy group, a methoxy group, an ethoxy group, a methoxy group substituted by at least one fluorine atom, a methylthio group, a methylthio group substituted by at least one fluorine atom, a formyl group, an acetyl group, an acetyl group substituted by at least one fluorine atom, an alkoxycarbonyl group having from 2 to 4 carbon atoms, a carbamoyl group, a cyano group, a nitro group, a methanesulfonyl group, an ethanesulfonyl group, a methanesulfonyl group substituted by at least one fluorine atom, or a sulfamoyl group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a methoxy group, an ethoxy group, a t-butoxy group, a methoxymethoxy group, an alkanoyloxymethoxy group in which the alkanoyl part has from 1 to 5 carbon atoms, a benzyloxy group, an alkanoyloxy group having from 1 to 12 carbon atoms, an alkenoyloxy group having 3 or 4 carbon atoms, a cycloalkylcarbonyloxy group having from 2 to 7 carbon atoms, a benzoyloxy group, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms, a benzyloxycarbonyloxy group, a phthalidyloxy group, a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group, a (5-phenyl-2-oxo-1,3-dioxolen-4-

yl)methoxy group, an amino group or a t-butoxycarbonylamino group.

51. The method of claim 48, wherein:

R¹ represents a halogen atom, a trifluoromethyl group, a hydroxy group, a difluoromethoxy group, a trifluoromethoxy group, a difluoromethylthio group, a trifluoromethylthio group, a formyl group, an acetyl group, a trifluoroacetyl group, a cyano group or a nitro group;

R² represents an alkanoyl group having from 2 to 6 carbon atoms, a substituted alkanoyl group which has from 2 to 6 carbon atoms and which is substituted by at least one fluorine atom, a cycloalkylcarbonyl group having from 4 to 7 carbon atoms, or a substituted cycloalkylcarbonyl group which is substituted by at least one fluorine atom; and

R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 10 carbon atoms, an alkoxycarbonyloxy group having from 2 to 5 carbon atoms or a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxy group.

52. The method of claim 48, wherein:

R¹ represents a fluorine or chlorine atom;

R² represents an acetyl group, a propionyl group, a substituted acetyl or propionyl group which is substituted by at least one fluorine atom, a cyclopropylcarbonyl group, cyclobutylcarbonyl group, or a substituted cyclopropylcarbonyl or cyclobutylcarbonyl group which is substituted by at least one fluorine atom;

R³ represents a hydrogen atom, a hydroxy group, a pivaloyloxymethoxy group, an alkanoyloxy group having from 2 to 6 carbon atoms or an alkoxycarbonyloxy group having from 2 to 5 carbon atoms; and

Y represents a sulfur atom.

53. The method of claim 48, wherein said blood platelet aggregation inhibitor is selected from the group consisting of:

5-(2-fluoro- α -propionylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(2-chloro- α -cyclopropylcarbonylbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-propionyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-butyryloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-valeryloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-hexanoyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

2-t-butoxycarbonyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-pivaloyloxymethoxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;

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5-(2-chloro- α -cyclopropylcarbonylbenzyl)-2-oxo-
2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its
tautomer;
5-(2-fluoro- α -propionylbenzyl)-2-oxo-2,4,5,6,7,7a-
hexahydrothieno[3,2-c]pyridine and its tautomer;
5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-2-oxo-
2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine and its
tautomer;
2-acetoxy -5-(2-chloro- α -cyclopropylcarbonylben-
zyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine;
5-[α -(2-fluorocyclopropylcarbonyl-2-fluorobenzyl)-
2-oxo-2,4,5,6,7,7a-hexahydrothieno[3,2-c]pyridine
and its tautomer;
2-acetoxy-5-[α -(2-fluorocyclopropylcarbonyl-2-
fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyri-
dine;
and pharmaceutically acceptable salts thereof.

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54. The compound of claim 1, wherein R¹ represents
a fluorine atom.

55. The compound of claim 1, wherein R¹ represents
a chlorine atom.

56. The compound of claim 1, wherein

R¹ represents a fluorine atom;

R² represents an acetyl group, a propionyl group, a
substituted acetyl or propionyl group which is
substituted by at least one fluorine atom, a cyclo-
propylcarbonyl group, cyclobutylcarbonyl group,
or a substituted cyclopropylcarbonyl or cy-
clobutylcarbonyl group which is substituted by at
least one fluorine atom;

R³ represents a hydrogen atom, a hydroxy group, a
privaloyloxymethoxy group, an alkanoyloxy group
having from 2 to 6 carbon atoms or an alkoxycar-
bonyloxy group having from 2 to 5 carbon atoms;
and

Y represents a sulfur atom.

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US005874581A

United States Patent [19]

Ataka et al.

[11] Patent Number: 5,874,581

[45] Date of Patent: Feb. 23, 1999

[54] 2-SILYLOXY-TETRAHYDROTHIENOPYRIDINE, SALT THEREOF AND PROCESS FOR PREPARING THE SAME

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[73] Assignee: UBE Industries, Ltd., Yamaguchi, Japan

[21] Appl. No.: 817,001

[22] PCT Filed: Oct. 4, 1995

[86] PCT No.: PCT/JP95/02023

§ 371 Date: Mar. 31, 1997

§ 102(e) Date: Mar. 31, 1997

[87] PCT Pub. No.: WO96/11203

PCT Pub. Date: Apr. 18, 1996

[30] Foreign Application Priority Data

Oct. 7, 1994 [JP] Japan 6-244141

[51] Int. Cl.⁶ C07D 471/04

[52] U.S. Cl. 546/114

[58] Field of Search 546/114

[56] References Cited

U.S. PATENT DOCUMENTS

4,740,510	4/1988	Badore et al.	514/291
5,190,938	3/1993	Badore et al.	514/215
5,288,726	2/1994	Koike et al.	514/301
5,436,242	7/1995	Koike et al.	514/229.2

FOREIGN PATENT DOCUMENTS

53950A1	6/1982	European Pat. Off.
57-120590	7/1982	Japan
61-246186	11/1986	Japan
3-130289	6/1991	Japan
6-41139	2/1994	Japan

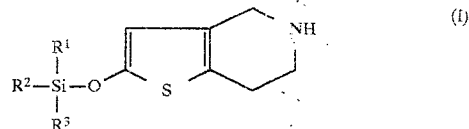
OTHER PUBLICATIONS

Greene TW and Wuts PGM. Protective Groups in Organic Synthesis. Second Edition. John Wiley & Sons, Inc. pp. 1,12,74,75,77,78,83, 1991.

Primary Examiner—Evelyn Huang
Attorney, Agent, or Firm—Jordan and Hamburg

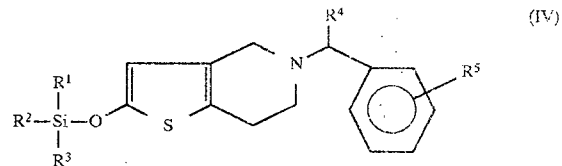
[57] ABSTRACT

A 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I):



wherein

R¹, R² and R³ each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group, and a salt thereof and a process for preparing the same, and a 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV):



wherein

R¹, R² and R³ represent the same meanings as described above; R⁴ represents a hydrogen atom, an alkoxy-carbonyl group having 2 to 10 carbon atoms, an acyl group having 2 to 10 carbon atoms or a cyclo-alkylcarbonyl group having 4 to 10 carbon atoms; and

R⁵ represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms,

which is useful as a synthetic intermediate of an antiplatelet medicine and an elastase inhibitor, etc., and a process for preparing the same.

15 Claims, No Drawings

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**2-SILYLOXY-
TETRAHYDROTHIENOPYRIDINE, SALT
THEREOF AND PROCESS FOR PREPARING
THE SAME**

This application is the national phase of PCT/JP95/02023, filed Oct. 4, 1995, published as WO 96/11203 on Apr. 18, 1996.

1. Technical field

The present invention relates to a 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, a salt thereof and a process for preparing the same.

2. Background art

2-Silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridines are useful as an intermediate for synthesizing tetrahydrothienopyridines numerous compounds of which have been developed as medicines, particularly an antiplatelet medicine and an elastase inhibitor.

As such a medicine in which an oxygen atom is introduced into 2-position of tetrahydrothienopyridine, there have been known (1) a 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative (see Japanese Patent Publication No. 39517/1990 and Japanese Provisional Patent Publication No. 246186/1986), (2) a 2-acyloxy-5-alkyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivative (see Japanese Provisional Patent Publication No. 130289/1991 and Japanese Provisional Patent Publication No. 41139/1994), etc.

As processes for preparing these compounds, the following preparation processes have been known.

(1) As a process for preparing the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivative, there has been known, for example, a preparation process using a method of acylating the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative according to the preparation process described in Japanese Provisional Patent Publication No. 130289/1991 or Japanese Provisional Patent Publication No. 41139/1994.

However, this preparation process is not an industrially satisfactory process because the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative is unstable under reaction conditions such that yield is low, and a process for preparing the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative is difficult for a reason mentioned in Preparation process (2) described below.

(2) As a process for preparing the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative, processes as shown below have been known.

(a) In Japanese Provisional Patent Publication No. 246186/1986, a process is disclosed for obtaining the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative by subjecting a 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative to a N-alkylation reaction.

However, the above-mentioned process (a) is not an industrially satisfactory process the stability of a starting material and a product are poor under the described reaction conditions, and yield is generally low.

(b) In Japanese Patent Publication No. 39517/1990, a process is disclosed for obtaining the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative by subjecting a 5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivative to an oxidation reaction.

However, the above-mentioned process (b) is not an industrially satisfactory process because only a specific stable alkyl group can be applied thereto.

(c) In Japanese Patent Publication No. 39517/1990, a process is disclosed for obtaining the 5-alkyl-5,6,7,7a-

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tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative by reacting a N-alkyl-3-alkoxycarbonylmethyl-tetrahydropyridin-4-one derivative with hydrogen chloride or hydrogen sulfide.

However, the above-mentioned process (c) is not an industrially satisfactory process because that harmful hydrogen chloride or hydrogen sulfide is used, and the preparation yield of a starting material is also poor.

(d) In Japanese Patent Publication No. 39517/1990, a process is disclosed for obtaining the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative by reacting a Grignard reagent of a 2-bromo-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine derivative with tert-butyl perbenzoate.

However, the above-mentioned process (d) is not an industrially satisfactory process because that numerous stages of reactions such as bromination, preparation of the Grignard reagent, the reaction with tert-butyl perbenzoate and acid decomposition are required, such that yield is low, and a N-substituent, which can be used for preparation of the Grignard reagent, is limited.

Therefore, the known preparation process (1) is not a satisfactory industrial process for obtaining the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine derivative, and all of the known preparation processes (2) [(a) to (d)] are not satisfactory industrial processes for obtaining the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one derivative.

**OBJECTS AND SUMMARY OF THE
INVENTION**

An object of the present invention is to provide a 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I), which is a novel compound, and also to provide an efficient process for preparing said medicine.

A further object of the present invention is to provide (1) a 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the following formula (IV) and a process for preparing said compound, and (2) an efficient process for preparing a 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the following formula (V) or a 5-alkyl-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one represented by the following formula (VI) from a 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the following formula (IV), by providing the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

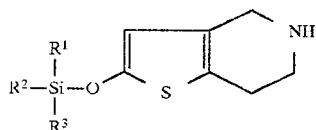
In view of such circumstances, the present inventors have found that a method of using the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as an intermediate is the most efficient as a process for preparing the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or the 5-alkyl-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one. As a result of intensive investigation of a synthetic process thereof, the present invention has been accomplished.

**DETAILED DESCRIPTION OF THE
INVENTION**

The first invention relates to a 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I).

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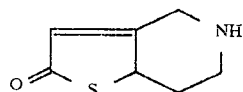


(I)

wherein

R¹, R² and R³ each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group, and a salt thereof.

The second invention relates to a process for preparing the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I), which comprises allowing a 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]-pyridin-2-one represented by the formula (II):



(II)

or a tautomer thereof to react with a halogenated silane represented by the formula (III):

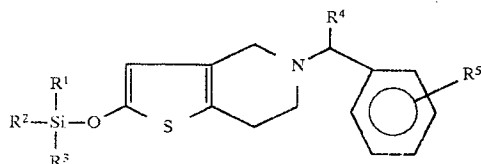


(III)

wherein

X represents a halogen atom, and R¹ to R³ represent the same meanings as described above, in the presence of a tertiary amine.

The third invention relates to a 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV):

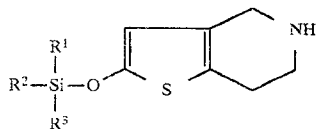


(IV)

wherein

R⁴ represents a hydrogen atom, an alkoxycarbonyl group having 2 to 10 carbon atoms, an acyl group having 2 to 10 carbon atoms or a cycloalkylcarbonyl group having 4 to 10 carbon atoms, R⁵ represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and R¹ to R³ represent the same meanings as described above.

The fourth invention relates to a process for preparing the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV), which comprises allowing the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I):

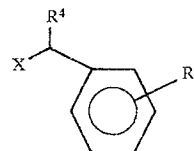


(I)

wherein

R¹ to R³ represent the same meanings as described above, or a salt thereof to react with a halogenated alkyl represented by the formula (VII):

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(VII)

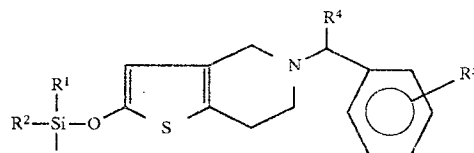
wherein

X and R⁴ to R⁵ represent the same meanings as described above,

in the presence of a tertiary amine.

Best mode for practicing the invention

The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I), which is the compound of the present invention, is converted into the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV):

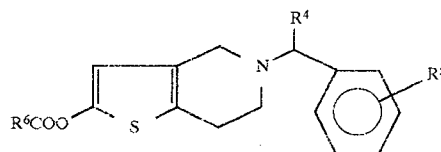


(IV)

wherein

R⁴ represents a hydrogen atom, an alkoxycarbonyl group having 2 to 10 carbon atoms, an acyl group having 2 to 10 carbon atoms or a cycloalkylcarbonyl group having 4 to 10 carbon atoms, R⁵ represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms, and R¹, R² and R³ represent the same meanings as described above, easily with a high yield.

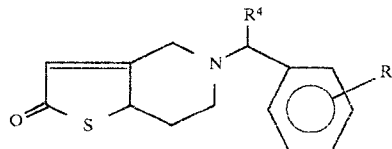
The converted 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) can be converted into a known 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V):



(V)

wherein

R⁶ represents an alkyl group having 1 to 10 carbon atoms, and R⁴ and R⁵ represent the same meanings as described above, or a known 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]-pyridin-2-one represented by the formula (VI):



(VI)

wherein

R⁴ and R⁵ represent the same meanings as described above, easily and efficiently with a high yield. A method thereof has also been developed by the present inventors.

As a result, it has been found that the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula

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(I) is an extremely useful precursor of the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V) and the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (VI).

Also, the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) is not only a useful intermediate of the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one, but also a novel compound which can be an antiplatelet medicine and an elastase inhibitor.

As a result, by using the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) as an intermediate, N-alkylation is carried out by simple operation. Through the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV), the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V) or the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (VI) can be obtained with a high yield. Thus, a preparation process in which yield is much higher than those of the conventional processes for preparing the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one, is rendered possible.

The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) and the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) are novel compounds.

In the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) and the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) in the compounds of the present invention, R¹, R² and R³ each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group.

The alkyl group having 1 to 10 carbon atoms represented by R¹, R² and R³ may include, for example, straight or branched alkyl groups such as a methyl group, an ethyl group, a propyl group (including an isomer), a butyl group (including the respective isomers), a pentyl group (including the respective isomers), a hexyl group (including the respective isomers), a heptyl group (including the respective isomers), an octyl group (including the respective isomers), a nonyl group (including the respective isomers) and a decyl group (including the respective isomers), etc. Alkyl groups having 1 to 5 carbon atoms are preferred, and a methyl group, an ethyl group, a propyl group (including an isomer) and a butyl group (including the respective isomers) are more preferred.

In the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) in the compounds of the present invention, the aryl group represented by R¹, R² and R³ may include, for example, a phenyl group, a tolyl group, a xylyl group, a biphenyl group, a naphthyl group, an anthryl group and a phenanthryl group, etc. An aryl group having 6 to 8 carbon atoms is preferred, and a phenyl group is more preferred.

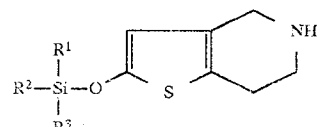
The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) in the compounds of the present invention can be converted into a salt, if necessary. Such a salt may include, for example, a salt of a mineral acid such as hydrochloric acid, sulfuric acid, etc., a salt of an organic sulfonic acid such as p-toluenesulfonic acid, methanesulfonic acid, etc., and a salt of an organic acid such as acetic acid, propionic acid, etc. Hydrochloric acid, sulfuric acid, p-toluenesulfonic acid and methanesulfonic acid are preferred, and hydrochloric acid and p-toluenesulfonic acid are more preferred.

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In the compounds of the present invention, the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) is preferably 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, 2-triisopropylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, and 2-(tert-butyldiphenylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof.

A specific example of the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine having the formula (I) in the compounds of the present invention may include, for example, compounds in the following Table 1.

TABLE 1

TABLE 1			
			
No.	R ¹	R ²	R ³
1	Me	Me	Me
2	Et	Et	Et
3	i-Pr	i-Pr	i-Pr
4	n-Pr	n-Pr	n-Pr
5	Me	Me	t-Bu
6	Ph	Ph	t-Bu

The abbreviations in the table have the following meanings.

Me: a methyl group

Et: an ethyl group

i-Pr: an isopropyl group

n-Pr: a normal propyl group

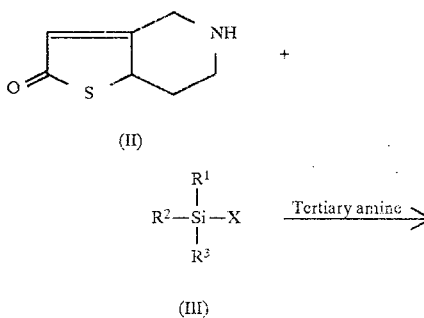
t-Bu: a tertiary butyl group

Ph: a phenyl group

Among the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridines represented by the above formula (I), 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, 2-(tert-butyldiphenylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, and 2-triisopropylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof are preferred.

The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) can be prepared by, for example, Reaction scheme (1) (hereinafter also referred to as Reaction 1) described below.

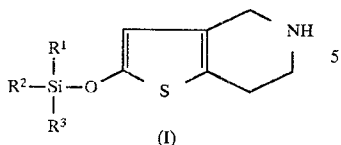
Reaction scheme (1)



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-continued
Reaction scheme (1)

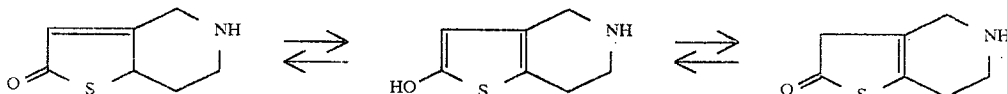


wherein

R^1 to R^3 and X represent the same meanings as described above.

The 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one (hereinafter also referred to as the 2-oxo-tetrahydrothienopyridine) to be used in the reaction of the present invention is a compound having a structural formula as shown below.

Structural formula of tautomers



Either of these tautomers can be used in the reaction of the present invention. Also, the 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one is generally stable in the state of a salt such that it is used mainly in the state of a salt in the reaction. The salt to be used may include, for example, a mineral acid salt such as hydrochloride, sulfate, etc., an organic sulfonic acid salt such as p-toluenesulfonate, methanesulfonate, etc., an organic acid salt such as acetate, propionate, etc., and the like.

Hydrochloride, sulfate, p-toluenesulfonate and methanesulfonate are preferred, and hydrochloride and p-toluenesulfonate are more preferred.

The above 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one, a tautomer thereof and salts thereof can be prepared according to the method described in Japanese Provisional Patent Publication No. 246187/1986, which is explained in more detail in Reference example.

The tertiary amine to be used in the reaction of the present invention may include, for example, trialkylmonoamines such as triethylamine, tributylamine, diisopropylethylamine, etc., trialkyldiamines such as diazabicyclooctane, diazabicycloundecane, tetramethylethyldiamine, etc., and the like. Trialkylmonoamines are preferred, and triethylamine and diisopropylethylamine are more preferred.

R^1 , R^2 and R^3 in the halogenated silane represented by the formula (III) to be used in the reaction of the present invention represent the same meanings as described above, and X represents a halogen atom.

The halogen atom represented by X in the halogenated silane represented by the formula (III) may include, for example, halogen atoms such as a fluorine atom, a chlorine atom, a bromine atom, an iodine atom, etc. A chlorine atom is preferred.

The halogenated silane having R^1 , R^2 , R^3 and X as described above may include, for example, trimethylchlorosilane, triethylchlorosilane, tripropylchlorosilane, triisopropylchlorosilane, tert-butyltrimethylchlorosilane, tert-butyltriethylchlorosilane, etc. In this case, from the point of the stability of the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine to be

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produced, preferred are triisopropylchlorosilane, tert-butyltrimethylchlorosilane, tert-butyltriethylchlorosilane, etc. which are sterically bulky. However, other starting material can be used in Reaction 3 shown below or the like if it is not isolated.

The tertiary amine to be used in the preparation process of the present invention is preferably triethylamine or diisopropylethylamine, and the halogenated silane represented by the formula (III) is preferably a compound selected from the group consisting of tert-butyltrimethylchlorosilane, tert-butyltriethylchlorosilane and triisopropylchlorosilane.

The reaction solvent to be used in the reaction of the present invention may include an ether type solvent such as tetrahydrofuran, diethyl ether, dioxane, etc., a chlorine type solvent such as methylene chloride, dichloroethane, etc., an aromatic hydrocarbon type solvent such as benzene, toluene, xylene, etc., a nitrile type solvent such as acetonitrile, propionitrile, benzonitrile, etc., an amide type solvent such

as dimethylformamide, dimethylacetamide, dimethylimidazolidone, etc., and the like. An ether type solvent, a chlorine type solvent and a nitrile type solvent are preferred, acetonitrile, dimethylacetamide and dimethylimidazolidone are more preferred, and acetonitrile is particularly preferred.

The reaction temperature in the reaction of the present invention is generally in the range of -20°C . to the boiling point of said solvent to be used, and 0°C . to 100°C . is preferred from the view of the stability of the reaction product.

The ratio (molar ratio) of the amounts of the respective reaction substrates to be used in the reaction of the present invention is theoretically the 2-oxo-tetrahydrothienopyridine: the tertiary amine: the halogenated silane=1:1:1. However, when extremely excess amounts of the tertiary amine and the halogenated silane based on the 2-oxo-tetrahydrothienopyridine are used, N-silylation proceeds simultaneously with O-silylation such that the yield of the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine which is a produced compound might be lowered. When the ratio (molar ratio) of the amounts of the tertiary amine and the halogenated silane to the 2-oxo-tetrahydrothienopyridine to be used is 1 or less, good results might be obtained in some cases.

With respect to the tertiary amine to be used in the reaction of the present invention, its amount to be used is generally such an amount that it is 0.5 to 3.0 mole, preferably such an amount that it is 0.5 to 2.0 mole, more preferably such an amount that it is 0.7 to 1.5 mole per 1 mole of the 2-oxo-tetrahydrothienopyridine.

Also, with respect to the halogenated silane represented by the formula (III) to be used in the reaction of the present invention, its amount to be used is generally such an amount that it is 0.5 to 3.0 mole, preferably such an amount that it is 0.5 to 2.0 mole, more preferably such an amount that it is 0.7 to 1.5 mole per 1 mole of the 2-oxo-tetrahydrothienopyridine.

The reaction concentration in the reaction of the present invention is not particularly limited, but the concentration of

TABLE 2

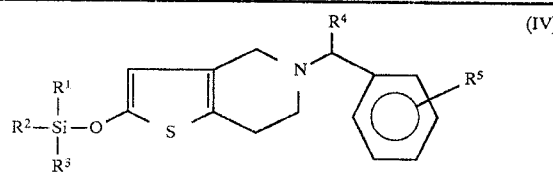
(IV)

No.	R ¹	R ²	R ³	R ⁴	R ⁵
7	Me	Me	Me	H	2-Cl
8	Me	Me	Me	H	2-F
9	Et	Et	Et	H	2-Cl
10	Et	Et	Et	H	2-F
11	i-Pr	i-Pr	i-Pr	H	2-Cl
12	i-Pr	i-Pr	i-Pr	H	2-F
13	t-Bu	Me	Me	H	2-Cl
14	t-Bu	Me	Me	H	2-F
15	t-Bu	Ph	Ph	H	2-Cl
16	t-Bu	Ph	Ph	H	2-F
17	n-Pr	n-Pr	n-Pr	H	2-Cl
18	n-Pr	n-Pr	n-Pr	H	2-F
19	t-Bu	Me	Me	CO ₂ Me	2-Cl
20	t-Bu	Me	Me	CO ₂ Et	2-Cl
21	Me	Me	Me	C(O)c-Pr	2-Cl
22	Me	Me	Me	C(O)c-Pr	2-F
23	Et	Et	Et	C(O)c-Pr	2-Cl
24	Et	Et	Et	C(O)c-Pr	2-F
25	t-Bu	Me	Me	C(O)c-Pr	2-Cl
26	t-Bu	Me	Me	C(O)c-Pr	2-F
27	t-Bu	Ph	Ph	C(O)c-Pr	2-Cl
28	t-Bu	Ph	Ph	C(O)c-Pr	2-F
29	i-Pr	i-Pr	i-Pr	C(O)c-Pr	2-Cl

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TABLE 2-continued

No.					
	R ¹	R ²	R ³	R ⁴	R ⁵
30	i-Pr	i-Pr	i-Pr	C(O)c-Pr	2-F
31	t-Bu	Me	Me	C(O)Me	2-Cl
32	t-Bu	Me	Me	C(O)Et	2-Cl
33	t-Bu	Me	Me	C(O)n-Pr	2-Cl
34	t-Bu	Me	Me	C(O)i-Pr	2-Cl
35	t-Bu	Me	Me	C(O)n-Bu	2-Cl

The abbreviations in the table represent the following meanings.

Me: a methyl group

Et: an ethyl group

n-Pr: a normal propyl group

c-Pr: a cyclopropyl group

i-Pr: an isopropyl group

n-Bu: a normal butyl group

t-Bu: a tertiary butyl group

Ph: a phenyl group

Among the compounds shown in the above Table 2, the following compounds are preferred.

2-(tert-Butyldimethylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldimethylsilyloxy)-5-(2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldimethylsilyloxy)-5-(α-methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldiphenylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-triisopropylsilyloxy-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldimethylsilyloxy)-5-(α-cyclopropyl-carbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-triisopropylsilyloxy-5-(α-cyclopropyl-carbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldimethylsilyloxy)-5-(α-cyclopropyl-carbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldiphenylsilyloxy)-5-(α-cyclopropyl-carbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, and

2-(tert-butyldiphenylsilyloxy)-5-(α-cyclopropyl-carbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Among the compounds shown in the above Table 2, the following compounds are more preferred.

2-(tert-Butyldimethylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldimethylsilyloxy)-5-(2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldimethylsilyloxy)-5-(α-methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-(tert-butyldiphenylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

2-triisopropylsilyloxy-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,

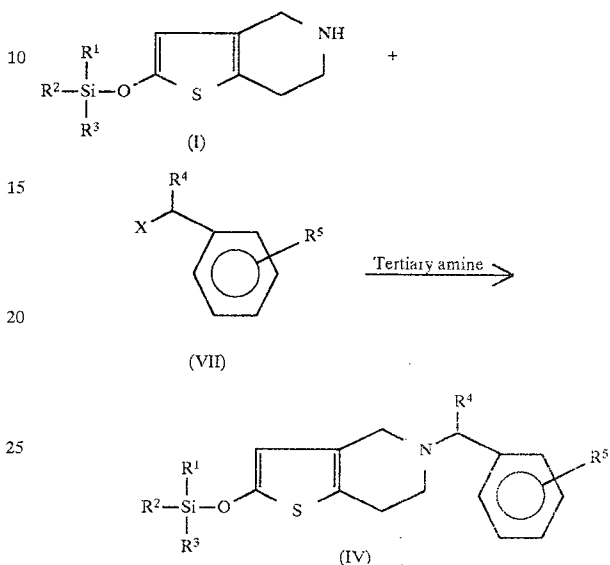
2-(tert-butyldimethylsilyloxy)-5-(α-cyclopropyl-carbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, and

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2-triisopropylsilyloxy-5-(α-cyclopropylcarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as described above can be prepared by, for example, Reaction scheme (2) shown below.

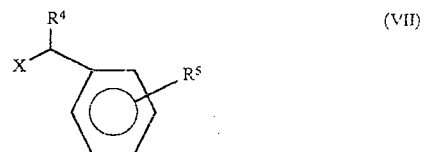
Reaction scheme (2)



wherein

R¹ to R⁵ and X represent the same meanings as described above.

The process (hereinafter also referred to as Reaction 2) for preparing the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV), represented by Reaction scheme (2) is a process for preparing the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV), in which the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (hereinafter also referred to as the 2-silyloxythienopyridine) represented by the formula (I) or a salt thereof is allowed to react with a halogenated alkyl represented by the formula (VII):



wherein

R⁴ and R⁵ represent the same meanings as described above, and X represents a halogen atom, in the presence of a tertiary amine.

In that case, the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) or a salt thereof to be used in Reaction 2 may be isolated from the reaction mixture after completion of the above reaction and used in a subsequent reaction, or may be used for a process (one pot reaction) in which the reaction mixture is allowed to react with the halogenated alkyl, without isolation.

The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof to be used in Reaction 2 may include, for example, the above compounds and salts thereof.

The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof as described above are preferably com-

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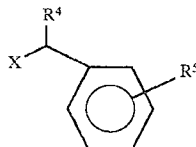
pounds having large steric hindrance such as 2-(tert-butyl)dimethylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, 2-(tert-butyl)diphenylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, and 2-triisopropylsilyloxy-5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof from the point that the produced 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine can be stably isolated.

Also, in the case of the process (one pot reaction) in which the reaction mixture is reacted with the halogenated alkyl without isolation, other 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof than the above compounds may be used.

R⁴ and R⁵ represented by the halogenated alkyl represented by the formula (VII) to be used in Reaction 2 may include R⁴ and R⁵ described above. X may include halogen atoms (a chlorine atom or a bromine atom is preferred).

A specific example of the compound having R⁴, R⁵ and X as described above may include compounds shown in the following Table 3.

TABLE 3

(VII)			
			
No.	R ⁴	R ⁵	X
36	H	2-Cl	Cl
37	H	2-Cl	Br
38	H	2-F	Cl
39	H	2-F	Br
40	CO ₂ Me	2-Cl	Cl
41	CO ₂ Et	2-Cl	Br
42	CO ₂ Me	2-F	Cl
43	CO ₂ Et	2-F	Br
44	C(O)Me	2-Cl	Cl
45	C(O)Et	2-Cl	Cl
46	C(O)n-Pr	2-Cl	Cl
47	C(O)Me	2-F	Cl
48	C(O)Et	2-F	Cl
49	C(O)n-Pr	2-F	Cl
50	C(O)n-Bu	2-F	Cl
51	C(O)Me	2-Cl	Br
52	C(O)Et	2-Cl	Br
53	C(O)n-Pr	2-Cl	Br
54	C(O)Me	2-F	Br
55	C(O)Et	2-F	Br
56	C(O)n-Pr	2-F	Br
57	C(O)n-Bu	2-F	Br
58	C(O)c-Pr	2-Cl	Cl
59	C(O)c-Pr	2-Cl	Br
60	C(O)c-Pr	2-F	Cl
61	C(O)c-Pr	2-F	Br

The abbreviations in the table represent the following meanings.

Me: a methyl group

Et: an ethyl group

n-Pr: a normal propyl group

c-Pr: a cyclopropyl group

n-Bu: a normal butyl group

Among the halogenated alkyls shown in the above Table 3, the following compounds are preferred.

2-Chlorobenzyl chloride, 2-fluorobenzyl chloride, 2-chloro- α -methoxycarbonylbenzyl bromide and 2-fluoro- α -cyclopropyl-carbonylbenzyl chloride.

The tertiary amine to be used in Reaction 2 may include, for example, trialkylmonoamines such as triethylamine,

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tributylamine, diisopropylethylamine, etc., trialkyldiamines such as diazabicyclooctane, diazabicycloundecane, tetramethylethyldiamine, etc., and the like. Trialkylmonoamines are preferred, and triethylamine, tributylamine and diisopropylethylamine are more preferred.

In Reaction 2, existence of an ammonium salt exhibits a reaction-accelerating action. Therefore, it is advantageous to carry out Reaction 2 subsequently to Reaction 1 because the tertiary ammonium salt produced in Reaction 1 can be utilized. Also, a quaternary ammonium salt is effective as a matter of course. An object thereof can be achieved not only by the produced tertiary ammonium salt but also by newly adding such a reaction-accelerating compound to the reaction system.

Such a reaction-accelerating compound to be added may include, for example, quaternary ammonium salts including a tetraalkylammonium halide having an alkyl group with 1 to 20 carbon atoms, such as tetramethylammonium chloride, tetramethylammonium bromide, tetraethylammonium chloride, tetraethylammonium bromide, tetrabutylammonium chloride and tetrabutylammonium bromide, a trialkylmonobenzylammonium halide having an alkyl group with 1 to 20 carbon atoms, such as trimethylbenzylammonium chloride and triethylbenzylammonium chloride, etc., an alkali metal bromide such as lithium bromide, sodium bromide, potassium bromide, cesium bromide, etc., and an alkali metal iodide such as lithium iodide, sodium iodide, potassium iodide, cesium iodide, etc.

With respect to the ammonium salt to be used in Reaction 2, its amount to be used is generally such an amount that it is 0.01 to 5 mole, preferably such an amount that it is 0.1 to 2 mole per 1 mole of the 2-silyloxythienopyridine.

With respect to the alkali metal bromide or the alkali metal iodide, its amount to be used is generally such an amount that it is 0.001 to 0.6 mole, preferably such an amount that it is 0.01 to 0.5 mole per 1 mole of the 2-silyloxythienopyridine.

The reaction solvent to be used in Reaction 2 may include an ether type solvent such as tetrahydrofuran, diethyl ether, dioxane, etc., a chlorine type solvent such as methylene chloride, dichloroethane, etc., an aromatic hydrocarbon type solvent such as benzene, toluene, xylene, etc., a nitrile type solvent such as acetonitrile, propionitrile, benzonitrile, etc., an amide type solvent such as dimethylformamide, dimethylacetamide, dimethylimidazolidone, etc., and the like. A ether type solvent, a chlorine type solvent and a nitrile type solvent are preferred, acetonitrile, dimethylacetamide and dimethylimidazolidone are more preferred, and acetonitrile is particularly preferred.

The reaction temperature in Reaction 2 is generally in the range of -20° C. to the boiling point of said solvent to be used, and 0° C. to 80° C. is preferred when the stabilities of the compounds to be used are taken into consideration.

The ratio (molar ratio) of the amounts of the respective reaction substrates to be used in Reaction 2 is generally the 2-silyloxythienopyridine: the tertiary amine: the halogenated alkyl=1:0.7 to 3.0:0.7 to 3. However, extremely excess amounts of the tertiary amine and the halogenated alkyl based on the 2-silyloxythienopyridine may be used.

With respect to the tertiary amine to be used in Reaction 2, its amount to be used is generally such an amount that it is 0.5 to 10 mole, preferably such an amount that it is 0.7 to 3.0 mole per 1 mole of the 2-silyloxythienopyridine.

With respect to the halogenated alkyl represented by the formula (VII) to be used in the reaction of the present invention, its amount to be used is generally such an amount that it is 0.5 to 10 mole, preferably such an amount that it is 0.7 to 3.0 mole per 1 mole of the 2-silyloxythienopyridine.

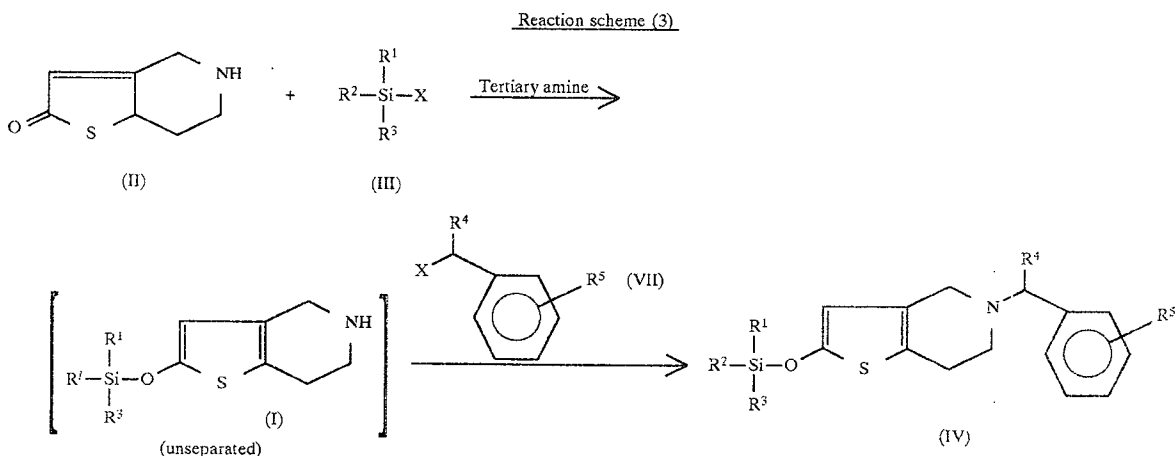
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The reaction substrates concentration in Reaction 2 is not particularly limited, but the reaction rate of the present reaction tends to be increased as the substrates concentration is higher. It is customary to heighten the concentration as far as possible, and the product concentration is preferably 10% or more.

Isolation of the desired compound from the reaction mixture can be carried out by common operation, but in consideration of the physical properties of the desired compound, crystallization, extraction, washing, column chromatography, etc. may be combined.

The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine can be obtained by the so-called one pot reaction in which a final product can be obtained from the tetrahydrothienopyridine without isolating the 2-silyloxythienopyrimidine which is an intermediate, which is represented by, for example, Reaction scheme (3) shown below.



wherein

R^1 , R^2 , R^3 , R^4 and R^5 represent the same meanings as described above.

The process (hereinafter also referred to as Reaction 3) for preparing the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, represented by Reaction scheme (3) is a process for preparing the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV), in which the 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (II) or a tautomer thereof is reacted with the halogenated silane represented by the formula (III) in the presence of a tertiary amine and the produced 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I) is reacted with the halogenated alkyl represented by the formula (VII), without isolation.

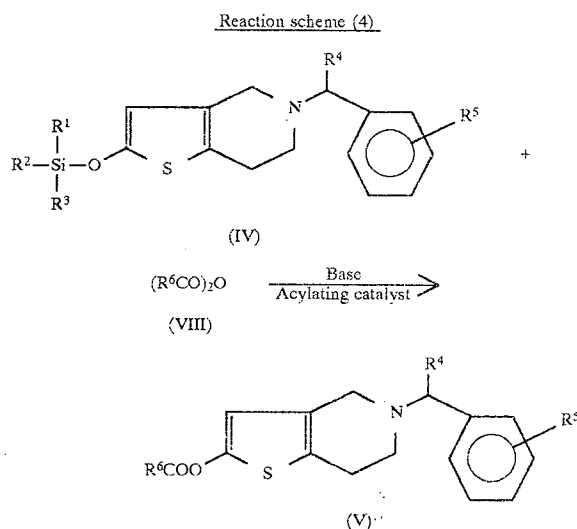
In Reaction 3, the reaction conditions such as the 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one or a tautomer thereof, the reaction substrates such as the tertiary amine, the reaction temperature, the reaction solvent, the ratio of the amounts of the reaction substrates to be used, the reaction concentration, etc. to be used in the step of producing the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine may be similar to those of the above process (Reaction 2). However, the halogenated silane to be used in Reaction 3 is preferably trimethylchlorosilane, triethylchlorosilane, tripropylchlorosilane, triisopropylchlorosilane, tert-

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butyldimethylchlorosilane or tert-butyldiphenylchlorosilane which is used in the above process (Reaction 1).

After completion of the reaction, isolation of the desired compound from the reaction mixture can be carried out by common operation, but in consideration of the physical properties of the desired compound, crystallization, extraction, washing, column chromatography, etc. may be combined.

From the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) obtained as described above, the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V) can be prepared by, for example, a process as shown in the following Reaction scheme (4).



wherein

R^1 to R^5 represent the same meanings as described above, and R^6 represents an alkyl group having 1 to 6 carbon atoms.

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The process for preparing the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, represented by Reaction scheme (4) (hereinafter also referred to as Reaction 4) is a process for preparing the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V), in which the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) with an acid anhydride represented by the formula (VIII):



(VIII)

wherein

R^6 represents the same meaning as described above, in the presence of a base and an acylating catalyst.

The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) and a salt thereof to be used in Reaction 4 can be prepared by the above Reaction 2. A specific example thereof may include, for example, the compounds shown in the above Table 2, and the specific compounds described above are more preferred.

R^6 in the acid anhydride represented by the formula (VIII) to be used in Reaction 4 may include, for example, straight or branched alkyl groups having 1 to 6 carbon atoms. A specific acid anhydride may include, for example, alkylcarboxylic acid anhydrides such as acetic anhydride, propionic anhydride, butyric anhydride, isobutyric anhydride, pivalic anhydride, valeric anhydride, isovaleric anhydride, etc. Acetic anhydride and pivalic anhydride are more preferred.

The base to be used in Reaction 4 is preferably a tertiary amine.

The tertiary amine may include, for example, trialkylamines such as triethylamine, tributylamine, diisopropylethylamine, etc., and triethylamine is preferred.

The acylating catalyst to be used in Reaction 4 may include, for example, 4-dialkylaminopyridines such as 4-dimethylaminopyridine, 4-diethylaminopyridine, 4-dipropylaminopyridine, etc., and 4-dimethylaminopyridine is preferred.

A specific example of the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V), which is obtainable by Reaction 4, may include, for example, compounds in the following Table 4.

TABLE 4

				(V)	
No.	R^4	R^5	R^6		
62	H	2-Cl	Me		
63	H	2-Cl	Et		
64	H	2-F	Me		
65	H	2-F	Et		
66	COOMe	2-Cl	Me		
67	COOMe	2-Cl	Et		
68	COOMe	2-F	Me		
69	COOMe	2-F	Et		
70	C(O)c-Pr	2-Cl	Me		
71	C(O)c-Pr	2-Cl	Et		
72	C(O)c-Pr	2-F	Me		
73	C(O)c-Pr	2-F	Et		
74	H	2-Cl	t-Bu		
75	H	2-F	t-Bu		
76	COOMe	2-Cl	t-Bu		

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TABLE 4-continued

				(V)	
No.	R^4	R^5	R^6		
77	COOMe	2-F	t-Bu		
78	C(O)c-Pr	2-Cl	t-Bu		
79	C(O)c-Pr	2-F	t-Bu		

The abbreviations in the table represent the following meanings.

Me: a methyl group

Et: an ethyl group

c-Pr: a cyclopropyl group

t-Bu: a tertiary butyl group

The reaction solvent to be used in Reaction 4 may include an ether type solvent such as tetrahydrofuran, diethyl ether, dioxane, etc., a chlorine type solvent such as methylene chloride, dichloroethane, etc., an aromatic type solvent such as benzene, toluene, xylene, etc., a nitrile type solvent such as acetonitrile, propionitrile, benzonitrile, etc., and an amide type solvent such as dimethylformamide, dimethylacetamide, dimethylimidazolidone, etc. A chlorine type solvent, an ether type solvent and a nitrile type solvent are preferred, and tetrahydrofuran and acetonitrile are more preferred.

The reaction temperature in Reaction 4 can be in the range of -50°C . to the boiling point of said solvent to be used and should be selected in consideration of the stabilities of the compounds to be used, etc., but it is preferably in the range of -20° to 80°C .

The molar ratio of the respective reaction substrates to be used in Reaction 4 is generally the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine: the tertiary amine: the acid anhydride=1:1:2. However, excess amount(s) of the tertiary amine and/or the acid anhydride may be used.

With respect to the tertiary amine to be used in Reaction 4, its amount to be used is preferably such an amount that it is 1 to 5 mole per 1 mole of the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

With respect to the acid anhydride, its amount to be used is generally preferably such an amount that it is 1 to 5 mole per 1 mole of the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

With respect to the acylating catalyst to be used in Reaction 4, its amount to be used is generally such an amount that it is 0.1 to 10 mole % per 1 mole of the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, and an excess amount thereof may also be used.

The reaction concentration in Reaction 4 is not particularly limited, but the reaction can be carried out generally at the concentration of the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine being in the range of 1 to 50%.

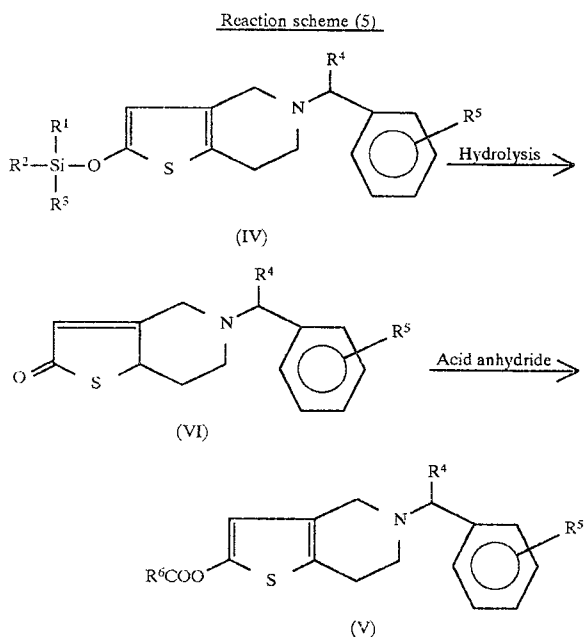
The reaction method in the reaction of the present invention can be a common method, and a method of adding a reaction reagent, etc. are not particularly limited.

Isolation of the desired compound from the reaction mixture can be carried out by common operation, but in consideration of the physical properties of the desired compound, crystallization, extraction, washing, column chromatography, etc. may be combined.

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Also, the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V) can be prepared by, for example, a preparation process represented by the following Reaction scheme (5) (hereinafter also referred to as Reaction 5).



wherein

R^1 , R^2 , R^3 , R^4 , R^5 and R^6 represent the same meanings as described above.

Reaction 5 is a process for preparing the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (V), in which the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) is hydrolyzed to produce the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (VI), followed by a further reaction with the acid anhydride represented by the formula (VIII).

The hydrolysis reaction to be carried out in Reaction 5 can be carried out in the presence of, for example, an organic carboxylic acid such as acetic acid, etc., an organic sulfonic acid such as p-toluenesulfonic acid, etc. and an acid in which these acids are combined. Water is not particularly required for the hydrolysis so long as an excess amount of the acid exists based on the 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine. The hydrolysis is easily finished for a reaction time of several minutes to 1 hour. The hydrolysis proceeds sufficiently at a reaction temperature of about room temperature (20° C.), and heating is not particularly required. It is considered that the reaction proceeds even at a low temperature of about -50° C., but it is not necessary to carry out the reaction at low temperature since any particular side reaction does not occur.

The organic solvent to be used for the hydrolysis to be carried out in Reaction 5 is not particularly limited, and a polar or non-polar organic solvent may be used. However, a chlorine type solvent such as methylene chloride, etc., an aromatic hydrocarbon type solvent, an ether type solvent and a ketone type solvent are preferred.

The 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (VI), obtainable by Reaction 5 is obtainable generally as a salt of the acid used. By selecting the organic solvent suitably, these salts are precipitated from the reaction system, whereby isolation is easy.

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The process for obtaining the 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV) by using the 5-alkyl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (VI) in Reaction 5 can be carried out according to the method described in Japanese Provisional Patent Publication No. 130289/1991 or Japanese Provisional Patent Publication No. 411139/1994. However, in general, a large amount of an acylating agent is required, the reaction yield is poor, and the reaction time is long.

Utilizability in industry

By using, as an intermediate, the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof which are the compounds of the present invention, the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine which is useful as a known antiplatelet medicine, can be obtained easily with a high yield.

Also, according to the preparation process of the present invention, by reacting the 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one or a tautomer thereof with the halogenated silane in the presence of the tertiary amine, the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof can be obtained easily with a high yield.

EXAMPLE

In the following, Examples are shown. Yields and reaction yields in Examples are yields of 2-silyloxy-tetrahydrothienopyridine derivatives (mole) based on 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate (mole).

Example 1

In 12 ml of acetonitrile were dissolved 808 mg (2.47 mmol) of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate and 225 mg (2.22 mmol) of triethylamine to obtain an acetonitrile solution. To the obtained acetonitrile solution was added 334 mg (2.22 mmol) of tertbutyldimethylchlorosilane, and the mixture was allowed to react under stirring at room temperature (20° C.) for 6 hours and then leaving to stand at room temperature (20° C.) for 12 hours.

The obtained reaction mixture was concentrated under reduced pressure to obtain a concentrate. To the obtained concentrate were added 40 ml of a phosphate buffer (pH 7.0) and 60 ml of ether, and separation operation was carried out to obtain an ether layer. After the obtained ether layer was dried over anhydrous magnesium sulfate, the volume of the layer was concentrated to about 1/3 by concentration under reduced pressure. Then, the concentrate was left to stand in a refrigerator (4° C.) for 24 hours to obtain colorless crystals. The obtained colorless crystals were filtered and dried under reduced pressure to obtain 777 mg (1.79 mmol) of 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-p-toluenesulfonate (p-toluenesulfonate of Compound No. 5) (yield: 72.4 %).

When HPLC analysis of the reaction mixture was carried out, the reaction yield of 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine was 97%.

Melting point: 85° to 86° C.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 0.21 (s, 6H), 0.96 (s, 9H), 2.13 (s, 1H), 2.35 (s, 1H), 2.89, 3.48, 4.11 (br, each 2H), 5.75 (s, 1H), 7.15, 7.62 (d, each 2H), 9.26 (br, each 2H).

HPLC analysis conditions

Column; ODS-80TM (4.6φ×150 mm)

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Eluent; acetonitrile: water=4:1 (v/v)+5 mM potassium dihydrogen phosphate
 Detector; UV (254 nm)
 Column temperature; 40° C.
 Flow rate; 1 ml/min

Example 2

In 10 ml of acetonitrile were dissolved 380 mg (1.16 mmol) of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate and 165 mg (1.28 mmol) of diisopropylethylamine to obtain an acetonitrile solution. To the obtained acetonitrile solution was added 193 mg (1.28 mmol) of tert-butyldimethylchlorosilane, and the mixture was allowed to react under stirring at room temperature (20° C.) for 3 hours.

When HPLC analysis of the obtained reaction mixture was carried out, a peak was observed at the same retention time as in Example 1, and production of 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine was confirmed. The reaction yield was 95%.

Example 3

In 1.5 ml of acetonitrile were dissolved 327 mg (1.00 mmol) of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate and 91 mg (0.90 mmol) of triethylamine to obtain an acetonitrile solution. To the obtained acetonitrile solution was added 274 mg (1.00 mmol) of tert-butyldiphenylchlorosilane, and the mixture was allowed to react under stirring at 25° C. for 10 hours.

To the obtained reaction mixture were added 10 ml of water and 20 ml of ether, and separation operation was carried out to obtain an ether layer. The obtained ether layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 405 mg (0.72 mmol) of 2-(tert-butyldiphenylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.p-toluenesulfonate (p-toluenesulfonate of Compound No. 6) as a pale yellow semi-solid product (yield: 72.0%).

MS spectrum (ET): 393, 364, 353, 273, 199, 135, 91

Example 4

In 3 ml of acetonitrile were dissolved 327 mg (1.00 mmol) of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate and 111 mg (1.10 mmol) of triethylamine to obtain an acetonitrile solution. To the obtained acetonitrile solution was added 212 mg (1.10 mmol) of triisopropylchlorosilane, and the mixture was allowed to react under stirring at 25° C. for 6 hours.

The obtained reaction mixture was concentrated under reduced pressure to obtain a concentrate. To the obtained concentrate were added 10 ml of water and 20 ml of ether, and separation operation was carried out to obtain an ether layer. The obtained ether layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 350 mg (0.72 mmol) of 2-triisopropylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.p-toluenesulfonate (p-toluenesulfonate of Compound No. 3) as colorless viscous liquid (yield: 72.0%).

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 1.05 to 1.11 (m, 21H), 2.28 (s, 3H), 2.82 (m, 3H), 3.42 (m, 2H), 4.05 (m, 2H), 5.71 (s, 1H), 7.07, 7.54 (d, each 2H), 9.12 (br, 2H).

In the following, a process for preparing 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate to be used in Reaction 1 is explained by Reference example 1.

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REFERENCE EXAMPLE

1: 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate

A mixture of 2.85 g of 5-trityl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one (see Japanese Provisional Patent Publication No. 246148/1986), 1.36 g of p-toluenesulfonic acid monohydrate and 50 ml of tetrahydrofuran was stirred at 50° C. for 2 hours. The precipitated solid was filtered, washed with 10 ml of tetrahydrofuran and then dried to obtain 2.28 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate (yield based on 5-trityl-5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one: 93%).

Melting point; 204° to 205° C. (decomposed)

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 1.76 (m, 1H), 2.28 (s, 3H), 2.60 (m, 1H), 3.24 (m, 1H), 3.35 (m, 1H), 3.43 (d, 1H), 3.98 (d, 1H), 4.72 (m, 1H), 6.46 (s, 1H), 7.12 (d, 2H), 7.50 (d, 2H), 9.07 (br, 1H).

In the following, Reaction 2 and Reaction 3 are explained by Examples 5 to 17. In this case, yield means yield of 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (mole) or 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (mole) based on 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate (mole).

Example 5

2-(tert-butyldimethylsilyloxy)-5-(2-chloro-benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 13)

A mixture of 5.00 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate, 2.47 g of tert-butyldimethylchlorosilane, 1.66 g of triethylamine and 15 ml of methylene chloride was stirred at room temperature (20° C.) for 3 hours. The produced 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.p-toluenesulfonate was not isolated, 2.40 g of 2-chlorobenzyl chloride and 3.02 g of triethylamine were added thereto, and the mixture was allowed to react under stirring at 40° C. for 8 hours.

After 15 ml of methylene chloride and 8 ml of water were added to the obtained reaction mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 15 ml of 0.2 N-hydrochloric acid and 8 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate =9:1) to obtain 3.98 g of 2-(tert-butyldimethylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a pale yellow oily product.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 0.20 (s, 6H), 0.96 (s, 9H), 2.71 (m, 2H), 2.86 (m, 2H), 3.48 (s, 2H), 3.81 (s, 2H), 5.75 (s, 1H), 7.19 to 7.57 (m, 4H).

Mass spectrum (CI): 394, 284, 240, 125, 73

Example 6

2-(tert-butyldimethylsilyloxy)-5-(2-fluoro-benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 14)

A mixture of 8.90 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one.p-toluenesulfonate, 4.40 g of tert-butyldimethylchlorosilane, 2.95 g of triethylamine and 27 ml of methylene chloride was stirred at room temperature (20° C.)

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for 3 hours. The produced 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-p-toluenesulfonate was not isolated, 5.00 g of 2-fluorobenzyl bromide and 5.36 g of triethylamine were added thereto, and the mixture was allowed to react.

The reaction mixture was refluxed by heat of reaction at the time of adding 2-fluorobenzyl bromide and triethylamine, but it was stirred as such at room temperature (20° C.) for 7 hours. After 13 ml of methylene chloride and 27 ml of water were added to the reaction mixture after stirring, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 25 ml of 0.2 N-hydrochloric acid and 13 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate =9:1) to obtain 7.48 g of 2-(tert-butyldimethylsilyloxy)-5-(2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a pale yellow oily product.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 0.19 (s, 6H), 0.95 (s, 9H), 2.70 (m, 2H), 2.82 (m, 2H), 3.43 (s, 2H), 3.76 (s, 2H), 5.74 (s, 1H), 7.02 to 7.48 (m, 4H).

Mass spectrum (CI): 378, 240, 109, 73

Example 7

2-(tert-butyldimethylsilyloxy)-5-(α-methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 19)

A mixture of 5.00 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate, 2.47 g of tert-butyldimethylchlorosilane, 1.66 g of triethylamine and 15 ml of methylene chloride was stirred at room temperature (20° C.) for 3 hours. The produced 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-p-toluenesulfonate was not isolated, 5.90 g of 2-chloro-α-methoxycarbonylbenzyl bromide and 3.02 g of triethylamine were added thereto, and the mixture was allowed to react.

The reaction mixture was heated to 37° C. by heat of reaction at the time of adding 2-chloro-α-methoxycarbonylbenzyl bromide and triethylamine, but it was stirred as such at room temperature (20° C.) for 4 hours and then left to stand overnight. After 15 ml of methylene chloride and 8 ml of water were added to the reaction mixture after leaving to stand, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 15 ml of 0.2 N-hydrochloric acid and 8 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate =9:1) to obtain 6.29 g of 2-(tert-butyldimethylsilyloxy)-5-(α-methoxycarbonyl-2-chloro-benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a pale yellow oily product.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 0.19 (s, 6H), 0.95 (s, 9H), 2.68 (t, 2H), 2.85 (t, 2H), 3.44 (d, 1H), 3.58 (d, 1H), 3.71 (s, 3H), 4.88 (s, 1H), 5.71 (s, 1H), 7.22 to 7.72 (m, 4H).

Mass spectrum (CI): 452, 392, 268, 240, 185, 125, 73

Example 8

2-(tert-butyldiphenylsilyloxy)-5-(2-chloro-benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 15)

A mixture of 2.00 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate, 1.84 g of tert-

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butyldiphenylchlorosilane, 0.66 g of triethylamine and 7 ml of methylene chloride was stirred at room temperature (20° C.) for 3 hours. The produced 2-(tert-butyldiphenylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-p-toluenesulfonate was not isolated, and 0.96 g of 2-chlorobenzyl chloride and 1.21 g of triethylamine were added thereto. The mixture was allowed to react at room temperature (20° C.) for 1.5 hours by further stirring and then left to stand overnight to obtain a reaction mixture.

After 6 ml of methylene chloride and 6 ml of water were added to the obtained reaction mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 6 ml of 0.2 N-hydrochloric acid and 6 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate =9:1) to obtain 1.99 g of 2-(tert-butyldiphenylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a pale yellow oily product.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 1.07 (s, 3H), 1.09 (s, 6H), 2.62 (t, 2H), 2.76 (t, 2H), 3.31 (s, 2H), 3.71 (s, 2H), 5.54 (s, 1H), 7.14 to 7.73 (m, 14H).

Mass spectrum (CI): 518, 364, 239, 197, 135, 125

Example 9

2-triisopropylsilyloxy-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 11)

A mixture of 2.00 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate, 1.29 g of triisopropylchlorosilane, 0.66 g of triethylamine and 7 ml of methylene chloride was stirred at room temperature for 3 hours. The produced 2-triisopropylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-p-toluenesulfonate was not isolated, 0.96 g of 2-chlorobenzyl chloride and 1.21 g of triethylamine were added thereto, and the mixture was allowed to react under further stirring at 40° C. for 10 hours.

After 6 ml of methylene chloride and 6 ml of water were added to the obtained reaction mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 6 ml of 0.2 N-hydrochloric acid and 6 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by silica gel column chromatography (eluent; hexane: ethyl acetate =9:1) to obtain 2.10 g of 2-triisopropylsilyloxy-5-(2-chloro-benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a pale yellow oily product.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 1.10 (d, 18H), 1.25 (qq, 3H), 2.70 (t, 2H), 2.83 (t, 2H), 3.45 (m, 2H), 3.78 (s, 2H), 5.77 (s, 1H), 7.17 to 7.55 (m, 4H).

Mass spectrum (CI): 436, 282, 157, 125, 73

Example 10

2-(tert-butyldimethylsilyloxy)-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 26)

To a mixture of 3.27 g of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate, 0.66 g of triethy-

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lamine and 7 ml of methylene chloride was added 1.58 g of tert-butyldimethylchlorosilane, and the mixture was stirred at 25° C. for 25 hours to obtain a mixed solution. To the obtained mixed solution were added 2.02 g of triethylamine and 2.12 g of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride, and the mixture was allowed to react under stirring at 40° C. for 12 hours.

After 20 ml of methylene chloride and 20 ml of 0.1 N-hydrochloric acid were added to the obtained reaction mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 20 ml of a 5% sodium hydrogen carbonate aqueous solution and 20 ml of water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. To the obtained residue was added 15 ml of acetonitrile, and the mixture was cooled to 0° C. to obtain precipitated crystals. The obtained precipitated crystals were filtered and dried to obtain 2.24 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydro-thieno [3,2-c]pyridine.

Melting point: 102.5° to 103.5° C.

Example 11-1

2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (a compound of Compound No. 26)

To a mixture of 4.91 g of 5,6,7,7a-tetrahydro-4H-thieno-[3,2-c]pyridin-2-one-p-toluenesulfonate, 2.37 g of tertbutyldimethylchlorosilane and 15 ml of methylene chloride was added 1.59 g of triethylamine, and the mixture was stirred at 25° C. for 1 hour to obtain a mixed solution. To the obtained mixed solution were added 3.04 g of triethylamine, 2.12 g of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride and 0.32 g of tetraethylammonium bromide, and the mixture was allowed to react under stirring at 45° C. for 8 hours.

After 8 ml of methylene chloride and 15 ml of water were added to the obtained reaction mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 15 ml of 0.2 N-hydrochloric acid and 15 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. To the obtained residue was added acetonitrile in an amount of 3.5 times the volume of the residue, and the mixture was stirred and cooled to 0° C. to obtain precipitated crystals. The obtained precipitated crystals were filtered and dried to obtain 3.9 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Example 11-2

2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (a compound of Compound No. 26)

In the same manner as in Example 11-1 except for changing the used amount of tetraethylammonium bromide to 1.58 g, a reaction and procedures were carried out to obtain 4.2 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Example 12

2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (a compound of Compound No. 26)

To a mixture of 4.91 g of 5,6,7,7a-tetrahydro-4H-thieno-[3,2-c]pyridin-2-one-p-toluenesulfonate, 2.37 g of tertbu-

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tyldimethylchlorosilane and 15 ml of methylene chloride was added 1.59 g of triethylamine, and the mixture was allowed to react under stirring at 25° C. for 1 hour.

To the obtained mixed solution were added 3.04 g of triethylamine and 3.85 g of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride, and the mixture was stirred at 45° C. for 2.5 hours to obtain a reaction mixture. After 8 ml of methylene chloride and 15 ml of water were added to the obtained reaction mixture, separation operation was carried out to separate an aqueous layer, whereby an organic layer was obtained. The obtained organic layer was combined with a methylene chloride solution obtained by extracting the separated aqueous layer again with 4 ml of methylene chloride to obtain a mixed organic layer. The mixed organic layer was washed with 15 ml of 0.2 N-hydrochloric acid and 15 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. To the obtained residue was added acetonitrile in an amount of 3.5 times the volume of the residue, and the mixture was stirred and cooled to 0° C. to obtain precipitated crystals. The obtained precipitated crystals were filtered and dried to obtain 2.93 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydro-thieno[3,2-c]pyridine.

Example 13

2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (a compound of Compound No. 26)

In the same manner as in Example 11-1 except for using 2.4 g of tetrabutylammonium bromide in place of tetraethylammonium bromide, a reaction and procedures were carried out to obtain 3.5 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Example 14

2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (a compound of Compound No. 26)

In the same manner as in Example 11-1 except for using 0.07 g of sodium iodide in place of tetraethylammonium bromide, a reaction and procedures were carried out to obtain 4.9 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Example 15

2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno-[3,2-c]pyridine (a compound of Compound No. 26)

A mixture of 442 mg of 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-p-toluenesulfonate, 1.0 ml of acetonitrile, 202 mg of triethylamine and 265 mg of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride was allowed to react under stirring at room temperature (20° C.) for 7 hours.

After 10 ml of ether and 10 ml of 0.1 N-hydrochloric acid were added to the obtained reaction mixture, separation

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operation was carried out to obtain an organic layer. The obtained organic layer was washed with 10 ml of a 5% sodium hydrogen carbonate aqueous solution and 10 ml of water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. To the obtained residue was added 1 ml of acetonitrile, and the mixture was stirred and cooled to 0° C. to obtain precipitated crystals. The obtained precipitated crystals were filtered and dried to obtain 112 mg of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Example 16

2-triisopropylsilyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 30)

To a mixture of 327 mg of 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one-p-toluenesulfonate, 111 mg of triethylamine and 3 ml of acetonitrile was added 212 mg of triisopropylchlorosilane, and the mixture was stirred at 45° C. for 6 hours to obtain a mixed solution. To the obtained mixed solution were added 202 mg of triethylamine and 265 mg of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride, and the mixture was stirred at 45° C. for 6 hours and then left to stand at room temperature (20° C.) for 13 hours to obtain a reaction mixture.

After 10 ml of methylene chloride and 10 ml of water were added to the obtained reaction mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 20 ml of 0.1 N-hydrochloric acid and 20 ml of an aqueous saturated sodium carbonate solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by thin layer chromatography (eluent; n-hexane: ethyl acetate =5:1) to obtain 105 mg of 2-triisopropylsilyloxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a colorless viscous product.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 0.83 (m, 2H), 1.02 to 1.10 (m, 21H), 1.25 (m, 2H), 2.27 (m, 1H), 2.71 (m, 2H), 2.89 (m, 2H), 3.46 (m, 2H), 4.82 (s, 1H), 5.73 (s, 1H), 7.11 to 7.50 (m, 4H).

Mass spectrum (CI): 488, 418, 310, 136

In the following, Reaction 4 is explained by Reference examples 2 to 10. In this case, yield means yield of 2-acyloxy-5-alkyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (mole) based on 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (mole).

Reference Example 2

2-acetoxy-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound 66)

A mixture of 3.00 g of 2-(tert-butyldimethylsilyloxy)-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, 1.35 g of triethylamine, 40 mg of 4-dimethylaminopyridine and 8 ml of acetonitrile was stirred at room temperature (20° C.) for 0.25 hour. Thereafter, 4 ml of acetonitrile in which 1.36 g of acetic anhydride was dissolved was added dropwise to the mixture, and the resulting mixture was allowed to react under further stirring at room temperature (20° C.) for 6 hours.

To the obtained reaction mixture was added 2.1 ml of a 10 mM aqueous potassium dihydrogen phosphate solution, and

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the mixture was stirred at room temperature (20° C.) for 1 hour. After 20 ml of water and 20 ml of methylene chloride were added to the mixture, separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 10 ml of water, 10 ml of an aqueous saturated sodium hydrogen carbonate solution and 10 ml of a saturated saline aqueous solution in this order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a residue. The obtained residue was purified by silica gel chromatography (eluent; hexane: methylene chloride =1:1) to obtain 1.72 g of 2-acetoxy-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine as a pale yellow oily product. When ethanol was added to this oily product and the mixture was stirred, the mixture was crystallized.

Melting point; 88.5° to 89.5° C.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 2.26 (s, 3H), 2.77 (m, 2H), 2.87 (m, 2H), 3.65 (d, 1H), 3.72 (s, 3H), 4.90 (s, 1H), 6.26 (s, 1H), 7.28 (m, 2H), 7.40 (m, 1H), 7.68 (m, 1H).

Mass spectrum (CI): 380, 320, 278, 196, 154, 126

Reference Example 3

2-pivaloyloxy-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 76)

Under ice water cooling (2° C.), 8 ml of an acetonitrile solution in which 2.50 g of pivalic anhydride was dissolved was added dropwise to a mixture of 3.02 g of 2-(tert-butyldimethylsilyloxy)-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, 1.35 g of triethylamine, 40 mg of 4-dimethylaminopyridine and 8 ml of acetonitrile, and the mixture was allowed to react under stirring at room temperature (20° C.) for 5 hours.

The obtained reaction mixture was cooled to -5° C., 2.1 ml of a 10 mM potassium dihydrogen phosphate aqueous solution was added thereto, and the mixture was stirred at room temperature (20° C.) for 1 hour. After 30 ml of methylene chloride and 8 ml of water were added to the mixture, the resulting mixture was separated to obtain an organic layer. The obtained organic layer was washed with 8 ml of an aqueous saturated sodium hydrogen carbonate solution and 8 ml of a saturated saline solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a concentrate. The obtained concentrate was purified by silica gel chromatography (eluent; hexane:methylene chloride =1:1) to obtain a pale yellow oily product. To the obtained pale yellow oily product was added 10 ml of ethanol, and the mixture was stirred to precipitate crystals. The precipitated crystals were filtered and dried to obtain 1.37 g of 2-pivaloyloxy-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Melting point; 118° to 120° C.

¹H-NMR (CDCl₃, 400 MHz, δ ppm) 1.31 (s, 9H), 2.77 (m, 2H), 2.88 (m, 2H), 3.53 (d, 1H), 3.65 (d, 1H), 3.72 (s, 3H), 4.90 (s, 1H), 6.26 (s, 1H), 7.24 to 7.31 (m, 2H), 7.40 (m, 1H), 7.68 (m, 1H).

Mass spectrum (CI): 422, 362, 278, 238, 154

Reference Example 4

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

A mixture of 1.0 g of 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-

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tetrahydrothieno[3,2-c]pyridine, 0.46 g of triethylamine, 14 mg of 4-dimethylaminopyridine and 3 ml of acetonitrile was stirred at room temperature (20° C.) for 0.25 hour. Thereafter, 2 ml of an acetonitrile solution in which 0.46 g of acetic anhydride was dissolved was added dropwise to the mixture, and the resulting mixture was allowed to react under further stirring at room temperature (20° C.) for 1 hour.

To the obtained reaction mixture was added 3.3 ml of a 10 mM aqueous potassium dihydrogen phosphate solution, and the mixture was stirred at room temperature (20° C.) for 1 hour to obtain precipitated crystals. The obtained precipitated crystals were filtered and dried to obtain 0.76 g of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Melting point; 120° to 121° C.

Reference Example 5

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

In the same manner as in Reference example 4 except for using 1.0 g of 2-(tert-isopropylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine in place of 2-(tert-butyltrimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, a reaction and procedures were carried out to obtain 0.70 g of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Reference Example 6

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

In the same manner as in Reference example 4 except for using 1.0 g of 2-(tert-butylphenylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine in place of 2-(tert-butyltrimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, a reaction and procedures were carried out to obtain 0.66 g of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Reference Example 7

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

A mixture of 6.7 g of 2-(tert-butyltrimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, 3.04 g of triethylamine, 0.2 g of 4-dimethylaminopyridine and 15 ml of tetrahydrofuran was stirred at room temperature (20° C.) for 0.25 hour. Thereafter, 7 ml of a tetrahydrofuran solution in which 4.7 g of acetic anhydride was dissolved was added dropwise to the mixture, and the resulting mixture was reacted under further stirring at room temperature (20° C.) for 4.5 hours.

The obtained reaction mixture was cooled to -10° C., 1.1 ml of a 10 mM potassium dihydrogen phosphate aqueous solution was slowly added dropwise thereto, and the mixture was stirred at -10° C. for 1 hour. Thereafter, a solution of 9.9 ml of a 10 mM aqueous potassium dihydrogen phosphate

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solution and 11 ml of ethanol was further added dropwise to the mixture, and the resulting mixture was stirred at -10° C. for 0.5 hour to obtain precipitated crystals. The obtained precipitated crystals were filtered and dried to obtain 5.1 g of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Reference Example 8

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

A mixture of 300 mg of 2-(tert-butyltrimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and 3 ml of acetic acid was allowed to react under stirring at room temperature (20° C.) for 0.25 hour.

To the obtained mixed solution was added 0.5 ml of an acetic acid solution in which 79 mg of acetyl chloride was dissolved, and the mixture was further stirred at room temperature (20° C.) for 4 hours. Thereafter, 552 mg of acetyl chloride was added to the mixture, and the resulting mixture was allowed to react under leaving to stand at room temperature (20° C.) overnight.

To the obtained reaction mixture were added 20 ml of toluene and 80 ml of an aqueous saturated sodium hydrogen carbonate solution, and separation operation was carried out to obtain an organic layer. The obtained organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a concentrate. The obtained concentrate was purified by silica gel chromatography (eluent; ethyl acetate: hexane = 1:3) to obtain 180 mg of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Reference Example 9

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

A mixture of 530 mg of acetic anhydride and 230 mg of p-toluenesulfonic acid monohydrate was stirred at room temperature (20° C.) for 0.5 hour to obtain a mixed solution. To the obtained mixed solution was added 500 mg of 2-(tert-butyltrimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, and the mixture was stirred at room temperature (20° C.) for 21 hours. Thereafter, 530 mg of acetic anhydride was added to the mixture, and the resulting mixture was allowed to react under further stirring for 50 hours.

To the obtained reaction mixture were added 20 ml of toluene and 30 ml of an aqueous saturated sodium hydrogen carbonate solution, and separation operation was carried out to obtain an organic layer. The obtained organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a concentrate. The obtained concentrate was purified by silica gel chromatography (eluent; ethyl acetate: hexane = 1:3) to obtain 310 mg of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

Reference Example 10

2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (a compound of Compound No. 72)

A mixture of 500 mg of 2-(tert-butyltrimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-

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tetrahydrothieno[3,2-c]pyridine, 5 ml of acetic acid and 230 mg of p-toluenesulfonic acid monohydrate was stirred at room temperature (20° C.) for 3 hours to obtain a mixed solution. To the obtained mixed solution was added 530 mg of acetic anhydride, and the mixture was allowed to react under stirring at room temperature (20° C.) for 88 hours.

To the obtained reaction mixture were added 20 ml of toluene and 120 ml of an aqueous saturated sodium hydrogen carbonate solution, and separation operation was carried out to obtain an organic layer. The obtained organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain a concentrate. The obtained concentrate was purified by silica gel chromatography (eluent; ethyl acetate: hexane =1:3) to obtain 360 mg of 2-acetoxy-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

In the following, a process for preparing a salt of a 5-alkyl-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one is explained by Reference examples 11-1 and 11-2.

Reference Example 11-1

5-(2-chlorobenzyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one-p-toluenesulfonate

A mixture of 8.23 g of 2-(tert-butyldimethylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, 4.31 g of p-toluenesulfonic acid monohydrate and 40 ml of methylene chloride was stirred at 40° C. for 2 hours to obtain precipitated crystals. The obtained precipitated crystals were filtered, washed with 20 ml of methylene chloride and dried under reduced pressure to obtain 7.85 g of 5-(2-chlorobenzyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one-p-toluenesulfonate.

Melting point; 224° to 225.5° C. (decomposed)

Reference Example 11-2

5-(2-chlorobenzyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one-oxalate

A mixture of 3.00 g of 5-(2-chlorobenzyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one-p-toluenesulfonate obtained in Reference example 11-1, 100 ml of water, 120 ml of methylene chloride and 1.41 g of sodium carbonate was allowed to react under stirring at 25° C. for 20 minutes.

The obtained reaction mixture was subjected to separation operation to separate an aqueous layer, whereby an organic layer was obtained. The obtained organic layer was washed twice with 100 ml of water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain a concentrate. The obtained concentrate was dissolved in 10 ml of acetone to obtain an acetone solution. To the obtained acetone solution was added 20 ml of acetone in which 0.66 g of oxalic acid was dissolved, and the mixture was stirred at room temperature (20° C.) for 1 hour to obtain precipitated crystals. The obtained precipitated crystals were filtered, washed with 30 ml of acetone and dried under reduced pressure to obtain 2.42 g of 5-(2-chlorobenzyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2-one-oxalate. The melting point of the crystals after recrystallization from ethanol was 163° C.

In the following, a process for preparing a halogenated alkyl is explained by Reference examples 12-1 to 12-2.

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Reference Example 12-1

2-fluoro- α -cyclopropylcarbonylbenzyl chloride
(Compound No. 60)

A mixture of 6.00 g of cyclopropyl 2-fluorobenzyl ketone and 40 ml of methylene chloride was stirred while cooling with ice to obtain a mixed solution. To the obtained mixed solution was added dropwise 4.45 g (33 mmol) of sulfuryl chloride while the liquid temperature was maintained to be not higher than 5° C. After the liquid temperature was gradually raised to room temperature (20° C.), the mixture was allowed to react under stirring for 1.5 hours.

To the obtained reaction mixture was added dropwise 30 ml of cold water (10° C.) extremely slowly at first. After dropwise addition, the mixture was stirred for 0.25 hour, and separation operation was carried out to obtain an organic layer. The obtained organic layer was washed with 30 ml of water, 50 ml of an aqueous saturated sodium hydrogen carbonate solution and 20 ml of water in this order, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain 7.1 g of an oily residue. As a result of carrying out gas chromatography analysis of the obtained residue, the content of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride in this residue was 80%.

Gas chromatography analysis conditions

Column; CBP10-M25-0.25 length 25 cm, film thickness 0.25 μ m, 0.22 mm ϕ

Column temperature; from 100° C. to 250° C. (temperature raised at 10° C./min)

Detector temperature; 270° C.

Carrier gas; He 150 ml/min

Split ratio; 100:1

Reference Example 12-2

2-fluoro- α -cyclopropylcarbonylbenzyl chloride

In the same manner as in Reference example 12-1 except for using 33 mmol of a chlorine gas in place of sulfuryl chloride, a reaction and procedures were carried out to obtain 2-fluoro- α -cyclopropylcarbonylbenzyl chloride. The content of 2-fluoro- α -cyclopropylcarbonylbenzyl chloride in the residue was 80%.

In the following, a process for preparing a cyclopropyl 2-halobenzyl ketone is explained by Reference examples 13-1 to 13-3.

Reference Example 13-1

cyclopropyl 2-fluorobenzyl ketone

To an isoropylmagnesium bromide solution prepared from 30.7 g of 2-bromopropane, 6.08 g of magnesium and 125 ml of tetrahydrofuran was added dropwise over 1 hour 75 ml of tetrahydrofuran in which 15.3 g of 2-fluorophenylacetic acid was dissolved. After completion of dropwise addition, the reaction temperature was raised from room temperature (20° C.) to reflux temperature (67° C.), and the mixture was further reacted for 3 hours to obtain a reaction mixture 1. The obtained reaction mixture 1 was cooled to 5° C., 20 ml of tetrahydrofuran in which 10.8 g of ethyl cyclopropanecarboxylate was dissolved was added dropwise thereto over 20 minutes. After completion of

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dropwise addition, the reaction temperature was raised from 5° C. to reflux temperature (68° C.), and the mixture was further reacted for 3 hours to obtain a reaction mixture 2. After the obtained reaction mixture 2 was cooled to room temperature (20° C.), 12 ml of water was added thereto, and the mixture was neutralized by adding 125 ml of 2 N-hydrochloric acid thereto to obtain a neutralized solution. The obtained neutralized solution was subjected to separation operation to separate an aqueous layer, whereby an organic layer was obtained. The separated aqueous layer was extracted with 10 ml of methylene chloride to obtain an extracted solution (twice). The methylene chloride layer in which the obtained organic layer and the extracted solution were combined was washed with 50 ml of an aqueous saturated sodium hydrogen carbonate solution, dried over anhydrous magnesium sulfate, concentrated under reduced pressure and evaporated under reduced pressure to obtain 9.5 g of cyclopropyl 2-fluorobenzyl ketone.

Boiling point 110 to 112° C./4 mmHg

Reference Example 13-2

cyclopropyl 2-fluorobenzyl ketone

In the same manner as in Reference example 13-1 except for using 19.6 g of 2-chloropropane in place of 2-bromopropane, reactions and procedures were carried out to obtain 9.5 g of cyclopropyl 2-fluorobenzyl ketone.

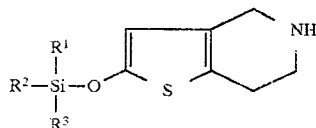
Reference Example 13-3

cyclopropyl 2-fluorobenzyl ketone

In the same manner as in Reference example 13-1 except for using 9.5 g of methyl cyclopropanecarboxylate in place of ethyl cyclopropanecarboxylate, reactions and procedures were carried out to obtain 9.5 g of cyclopropyl 2-fluorobenzyl ketone.

We claim:

1. A 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I):



wherein

R¹, R² and R³ each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group, or a salt thereof.

2. The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a salt thereof according to claim 1, wherein R¹ to R³ are alkyl groups having 1 to 5 carbon atoms or phenyl groups.

3. The 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof according to claim 1, wherein said compound is selected from the group consisting of:

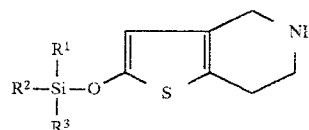
2-(tert-butyl dimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof,

2-triisopropylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, and

2-(tert-butyl diphenylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof.

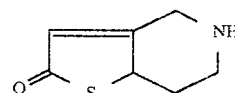
4. A process for preparing a 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I):

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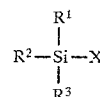


wherein

R¹, R² and R³ each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group; which comprises allowing a 5,6,7,7a-tetrahydro-4H-thieno[3,2-c]pyridin-2-one represented by the formula (II):



or a tautomer thereof to react with a halogenated silane represented by the formula (III):



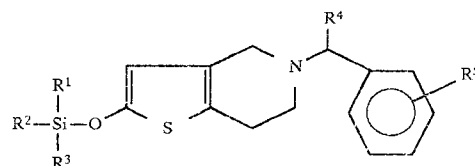
wherein

R¹, R² and R³ represent the same meanings as described in claim 1, and X represents a halogen atom, in the presence of a tertiary amine.

5. The preparation process according to claim 4, wherein the tertiary amine is triethylamine or diisopropylethylamine.

6. The preparation process according to claim 4, wherein the halogenated silane is a compound selected from the group consisting of tert-butyl dimethylchlorosilane, tert-butyl diphenylchlorosilane and triisopropylchlorosilane.

7. A 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV):



wherein

R¹, R² and R³ each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group; R⁴ represents a hydrogen atom, an alkoxy carbonyl group having 2 to 10 carbon atoms, an acyl group having 2 to 10 carbon atoms or a cycloalkyl carbonyl group having 4 to 10 carbon atoms; and R⁵ represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms.

8. The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine according to claim 7, wherein R¹ to R³ are alkyl groups having 1 to 5 carbon atoms or phenyl groups.

9. The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine according to claim 7, wherein R⁴ is selected from the group consisting of a hydrogen atom, an alkoxy carbonyl group wherein the alkyl group portion has 1 to 5 carbon atoms, an acyl group wherein the alkyl group portion has 1 to 5 carbon atoms and a cycloalkyl carbonyl group wherein the cycloalkyl group portion has 3 to 6 carbon atoms.

10. The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine according to claim 7, wherein R⁵ is selected from

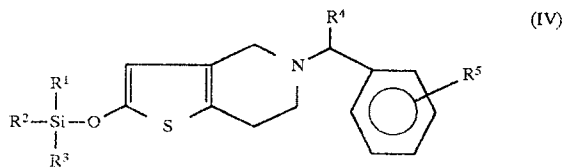
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the group consisting of a fluorine atom, a chlorine atom, an alkyl group having 1 to 3 carbon atoms and an alkoxy group having 1 to 3 carbon atoms.

11. The 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine according to claim 7, wherein said compound is selected from the group consisting of:

- 2-(tert-butyldimethylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-(tert-butyldimethylsilyloxy)-5-(2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-(tert-butyldimethylsilyloxy)-5-(α -methoxycarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-(tert-butyldiphenylsilyloxy)-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-triisopropylsilyloxy-5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-triisopropylsilyloxy-5-(α -cyclopropylcarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-(tert-butyldimethylsilyloxy)-5-(α -cyclopropylcarbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine,
- 2-(tert-butyldiphenylsilyloxy)-5-(α -cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, and
- 2-(tert-butyldiphenylsilyloxy)-5-(α -cyclopropylcarbonyl-2-carbonyl-2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine.

12. A process for preparing a 5-alkyl-2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (IV):

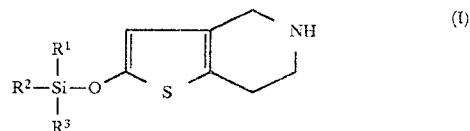


wherein

R^1 , R^2 and R^3 each independently represent an alkyl group having 1 to 10 carbon atoms or an aryl group; R^4 represents a hydrogen atom, an alkoxycarbonyl group having 2 to 10 carbon atoms, an acyl group having 2 to 10 carbon atoms or a cycloalkylcarbonyl group having 4 to 10 carbon atoms; R^5 represents a halogen atom, an alkyl group having 1 to 4 carbon atoms or an alkoxy group having 1 to 4 carbon atoms;

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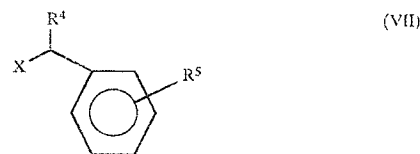
which comprises allowing a 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine represented by the formula (I):



wherein

R^1 , R^2 and R^3 represent the same meanings as described in claim 1,

or a salt thereof to react with a halogenated alkyl represented by the formula (VII):



wherein

R^4 and R^5 represent the same meanings as described in claim 7, and X represents a halogen atom, in the presence of a tertiary amine.

13. The preparation process according to claim 12, wherein the 2-silyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine compound is selected from the group consisting of: 2-(tert-butyldimethylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, 2-triisopropylsilyloxy-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof, and 2-(tert-butyldiphenylsilyloxy)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine and a salt thereof.

14. The preparation process according to claim 12, wherein the halogenated alkyl is a compound selected from the group consisting of 2-chlorobenzyl chloride, 2-fluorobenzyl chloride, 2-chloro- α -methoxycarbonylbenzyl bromide and 2-fluoro- α -cyclopropylcarbonylbenzyl chloride.

15. The preparation process according to claim 12, wherein the tertiary amine is triethylamine, tributylamine or diisopropylethylamine.

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