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(54) Title  
METHOD FOR MAKING CERTAIN PYRANO(3',4':6,7)INDOLIZINO(1,2-B)QUINOLINONES

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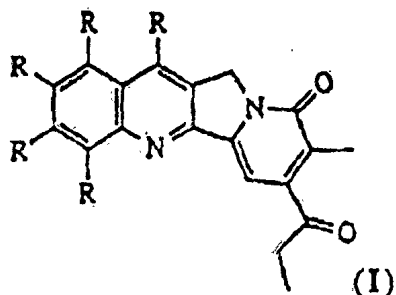
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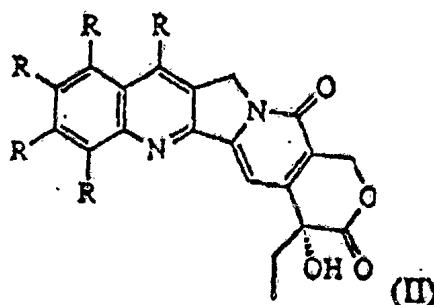
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(57) Claim

1. A method for making a 8-methyl-7-(1-oxopropyl)indolizino[1,2-b]quinolin-9(11H)-one of formula I



where R represents hydrogen or another substituent, which method comprises heating to about 150°C-200°C a 4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-3,14(4H,12H)-dione of the formula II



neat or in a solvent.

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| <b>(51) International Patent Classification <sup>5</sup> :</b><br><b>C07D 471/22</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 92/06095</b><br><b>(43) International Publication Date:</b> 16 April 1992 (16.04.92)                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>(21) International Application Number:</b> PCT/US91/06869<br><b>(22) International Filing Date:</b> 23 September 1991 (23.09.91)<br><b>(30) Priority data:</b><br>589,848 28 September 1990 (28.09.90) US<br><b>(71) Applicant (for all designated States except US):</b> SMITH-KLINE BEECHAM CORPORATION [US/US]; 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406 (US).<br><b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only) :</b> FORTUNAK, Joseph, Marian [US/US]; 526 Westfield Drive, Exton, PA 19341 (US). MELLINGER, Mark [US/US]; 262 West Broad Street, Telford, PA 18969 (US). WOOD, Jeffery, Lee [US/US]; 1640 Winchester Drive, Blue Bell, PA 19422 (US). |           | <b>(74) Agents:</b> STERCHO, Yuriy, P. et al.; Smithkline Beecham Corporation, Corporate Patents - U.S. (UW2220), 709 Swedeland Road, King of Prussia, PA 19406 (US).<br><b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.<br><br><b>Published</b><br>With international search report.<br><br><b>653173</b> |
| <b>(54) Title:</b> METHOD FOR MAKING CERTAIN PYRANO[3',4':6,7]INDOLIZINO[1,2-b]QUINOLINONES<br><br><b>(57) Abstract</b><br><br>A method for making 8-methyl-7-(1-oxopropyl)indolizino[1,2-b]quinolin-9(11H)-ones from 4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-3,14(4H, 12H)-diones.                                                                                                                                                                                                                                                                                                                                                                                                  |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

# METHOD FOR MAKING CERTAIN PYRANO[3'4':6,7] INDOLIZINO-[1,2,-b]QUINOLINONES

## Scope of the Invention

This invention relates to a method for making certain 8-methyl-  
5 7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-ones from 4-ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4*H*,12*H*)-diones.

## Background

Certain 1*H*-pyrano[3'4',6,7]indolizino[1,2-*b*]quinolinones are  
10 know to have cytotoxic and antiviral activity. Camptothecin {4-ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7] indolizino[1,2-*b*]quinolin-3,14(4*H*,12*H*)-dione} is an example of one such compound. It is a water-insoluble, cytotoxic alkaloid produced by Camptotheca  
accuminata plants indigenous to China and Nothapodytes foetida  
15 plants indigenous to India. Camptothecin and a few close congeners thereof are the only class of compounds known to inhibit eukaryotic topoisomerase I. Camptothecin (and its known congeners) have no effect on topoisomerase II and none of the known topoisomerase II inhibitors has any significant effect on topoisomerase I.

20 Certain modifications to the camptothecin molecule have produced compounds which have antiviral activity, but are not cytotoxic or have little cytotoxicity. One of these modifications is that of opening the E ring in camptothecin in a way which gives a 8-methyl-7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-one. These  
25 compounds and analogs have useful antiviral activity. Such compounds are disclosed in co-pending U.S. application Serial No. 07/589,643, of Patrick L. Burk, et al., filed on even date herewith.

This invention provides a method for making certain 8-methyl-7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-ones. These ketones  
30 can be used for preparing other antiviral agents where the indolizino or quinolino portions of these compounds are substituted.

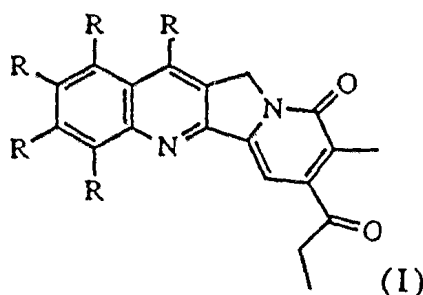
## Summary of The Invention

This invention relates to a method for making a 8-methyl-7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-one of formula I,

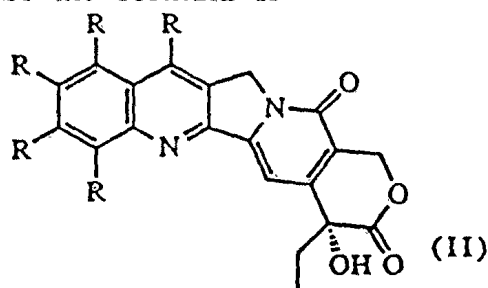
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which method comprises heating to about 100 C° or higher a 4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-3,14(4H,12H)-dione of the formula II



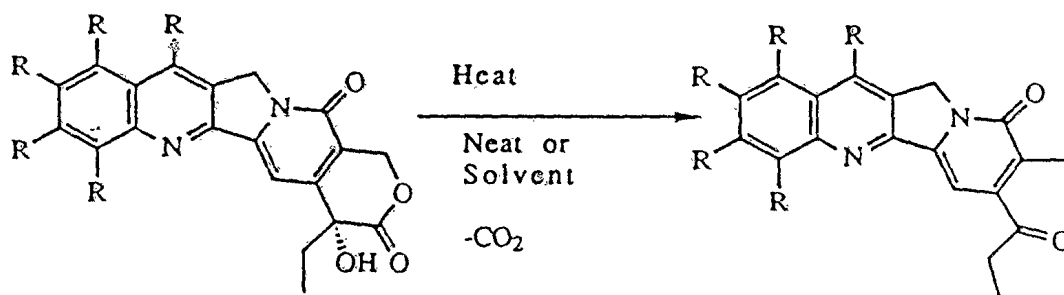
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neat or in a solvent.

### Specific Embodiments

This reaction is useful for making compounds of formula I which is unsubstituted, or substituted with one or more substituents, represented by the R designation in formula I. The only limitation is that the R substituent, if it is other than hydrogen, is not affected during the heating process used to make formula I.

Graphically it can be illustrated as follows.



15

This efficient process can be carried by heating the compound either neat or in an appropriate solvent. Useful temperatures are those at which the reaction proceeds at a reasonable rate and which do not pyrolytically degrade another site on the ring of formula II, or degrades an R substituent. Too low a temperature, while it may cause loss of CO<sub>2</sub>, will proceed so slowly as to be of no practical use. It is preferred that a temperature in excess of 100°C be used for efficient operation of this reaction. The only limitation on temperature is that



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operation of this reaction. The only limitation on temperature is that it not be so high as to cause unwanted degradation of the molecule. The most preferred temperature range is between about 150-200°C.

Solvents may be used in practicing this invention. There is no limitation on what solvents may be used other than it must have a boiling point at or higher than the temperature at which the reaction is to be carried out. Secondly, the solvent itself must be inert with respect to the reaction. In other words, the solvent must not interfere with the reaction in the sense of reacting with the molecule or in some means having an untoward or deleterious affect on the reaction or reactant.

Two preferred solvents are N,N-dimethylformamide and triethylene glycol dimethyl ether (triglyme).

### Examples

#### Example 1

##### 8-methyl-7-(1-oxopropyl)indolizino[1,2-b]quinolin-9(11H)-one

A sample of 4.6 g of 4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-3,14(4H,12H)-dione [(20 S) camptothecin] was stirred with 46 ml of N,N-dimethylformamide. The suspension was heated at reflux, and the disappearance of starting material was monitored by HPLC (C18 reverse phase column, 20-25% acetonitrile:water mobile phase, perchlorate buffer at pH approximately 3.0). The reaction was monitored by UV detection at a wavelength of 228 nm. The only responses detected under these conditions were a peak for N,N-dimethylformamide near the solvent front, a peak for the starting material and a peak for the desired product with a retention time of approximately 3.2 relative to the starting material. The reaction was heated until consumption of the starting material was complete (approximately 8 days). After cooling to ambient temperature the solid product was collected by filtration, and washed with methanol. After drying under vacuum to a constant weight 3.48 g (87%) of product, m.p. 233-234°C was obtained.

#### Example 2

##### 10-hydroxy-8-methyl-7-(1-oxopropyl)indolizino[1,2-b]quinolin-9(11H)-one

A stirred suspension of 4.0 g of 10-hydroxycamptothecin in 50 ml of triethylene glycol dimethyl ether (triglyme) was heated at

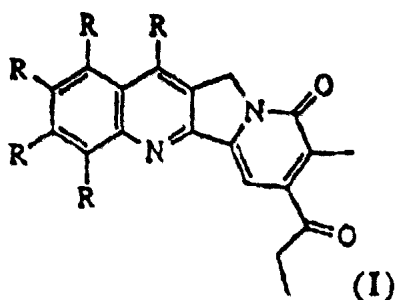
approximately 200 degrees C. The reaction was monitored by HPLC using the conditions of the preceding example. A relative retention time of approximately 3.05 was obtained for the product versus the starting material. The reaction  
5 suspension gradually formed a golden yellow solution over about 2.5 hours. After 6.5 hours the starting material was completely consumed. The reaction was cooled to ambient temperature with stirring over 17 hours. The suspension was diluted with 100 ml of diethyl ether, and after stirring for  
10 an additional 2 hours, the solid product was collected by filtration and dried to a constant weight. The recovered product, m.p. > 315°C, weight 3.35 g (95%).

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

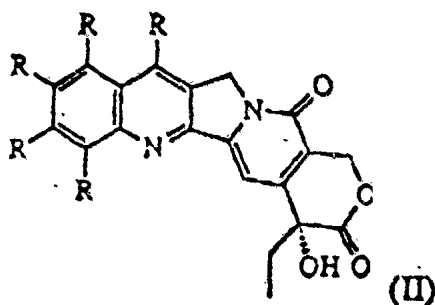


THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for making a 8-methyl-7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-one of formula I



where R represents hydrogen or another substituent, which method comprises heating to about 150°C-200°C a 4-ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-3,14(4*H*,12*H*)-dione of the formula II



neat or in a solvent.

2. The method of claim 1 where the product is 8-methyl-7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-one.

3. The method of claim 2 which is carried out in *N,N*-dimethylformamide at about reflux.

4. The method of claim 1 where one or more of the R groups is other than hydrogen.

5. The method of claim 4 which is carried out in a triglyme at a temperature of about 200°C.



6. A method for making a 8-methyl-7-(1-oxopropyl)indolizino[1,2-*b*]quinolin-9(11*H*)-one of formula I, substantially as hereinbefore described with reference to the Examples.

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DATED this 18th day of July, 1994.

10 SMITHKLINE BEECHAM CORPORATION  
By its Patent Attorneys  
DAVIES COLLISON CAVE



# INTERNATIONAL SEARCH REPORT

International Application No. **PCT/US91/06869**

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| <b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                           |                                                           |
| According to International Patent Classification (IPC) or to both National Classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                           |                                                           |
| IPC(5): <b>C07D 471/22</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                           |                                                           |
| US CL : <b>546/70</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                           |                                                           |
| <b>II. FIELDS SEARCHED</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                           |                                                           |
| Minimum Documentation Searched ?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                           |                                                           |
| Classification System :                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Classification Symbols                                                                                                    |                                                           |
| <b>US</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>546/70, 48</b>                                                                                                         |                                                           |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                           |                                                           |
| <b>Chemical Abstracts Service Structural Database</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                           |                                                           |
| <b>III. DOCUMENTS CONSIDERED TO BE RELEVANT *</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                           |                                                           |
| Category *                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Citation of Document, ** with indication, where appropriate, of the relevant passages **                                  | Relevant to Claim No. **                                  |
| <b>X</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>Kingsbury, "Chemical Rearrangement of Camptothecin", Tetrahedron Lett. 29(52), 6847-50, 1988. See entire document.</b> | <b>1-5</b>                                                |
| <b>A</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>Hertzberg, "Modification of the Hydroxylactone Ring" J. Med. Chem. 32(3), 715-20, 1989. See entire document.</b>       | <b>1-5</b>                                                |
| <p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> |                                                                                                                           |                                                           |
| <b>IV. CERTIFICATION</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                           |                                                           |
| Date of the Actual Completion of the International Search                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                           | Date of Mailing of this International Search Report       |
| <b>07 November 1991</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                           | <b>06 DEC 1991</b>                                        |
| International Searching Authority                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                           | Signature of Authorized Officer                           |
| <b>ISA/US</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                           | <i>Andre Robinson</i><br><b>Catherine S. Kilby Scalzo</b> |