COMMISSIONER'S DECISION SUMMARY

C.D. 1212 ....Application No. 546,105 (F01, O)

Certain claims rejected as disclosing known compounds.

The application disclosed a process of separating leucovorin into its constituent optical isomers. Claims directed to these optical isomers were rejected on the grounds that the isomers were already known. The Board recommended that the rejection be reversed since the references cited in the opinion of the Board did not justify a finding of either anticipation or obviousness in the case.

IN THE CANADIAN PATENT OFFICE

DECISION OF THE COMMISSIONER OF PATENTS

Patent application number 546,105, having been rejected under Subsection 47(2) of the Patent Rules, the Applicant asked that the Final Action of the Examiner be reviewed. The rejection has been considered by the Patent Appeal Board and by the Commissioner of Patents. The findings of the Board and the decision of the Commissioner are as follows:

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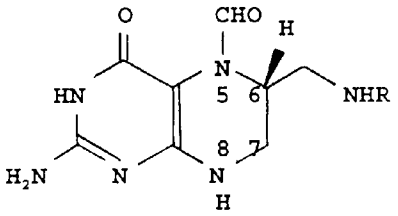
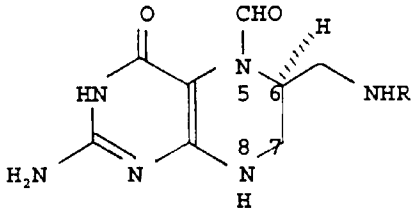
This decision deals with a request that the Commissioner of Patents review the Examiner's Final Action on patent application number 546,105 (Class 260-242.13) which was filed on September 3, 1987. The Applicant is the University of Strathclyde, assignee of inventors Hamish C.S. Swan Wood, Colin J. Suckling and Lilias Rees and the invention is entitled "OPTICALLY ACTIVE COMPOUNDS". The Examiner in charge issued a Final Action on March 13, 1992 rejecting certain claims of the application in view of twelve references and the Applicant replied on September 11, 1992 requesting that the refusal be reviewed by the Commissioner of Patents.

The invention is directed to the preparation of substantially pure diastereoisomers of derivatives of tetrahydrofolic acid and the use of such diastereoisomers. Methotrexate is an inhibitor of the enzyme dihydrofolate reductase which prevents the conversion of deoxyuridylate into thymidylate. It thus prevents the biosynthesis of DNA and is commonly used in cancer therapy. However methotrexate is toxic to normal cells as well as to cancerous cells and hence a "rescue agent" is often administered some 12 to 24 hours after treatment with a high dose of methotrexate. Leucovorin (5-formyltetrahydrofolic acid) is one such commonly used rescue agent for methotrexate.

Leucovorin has two chiral centres and the product commercially available at the time of filing of the application (Wellcovorin from the Wellcome Foundation) is composed of equal amounts of compounds of the formulae 1a and 1b, in the form of their calcium salts, which compounds have the R and S stereochemistry respectively at C-6, i.e. Wellcovorin is a racemic mixture of two optical isomers.

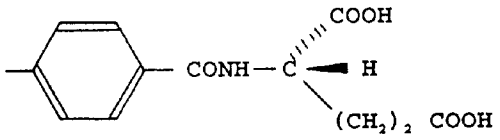


1a



1b

where R is



Since it has been reported that only the (6S) diastereoisomer (1b) is effective as a rescue agent for methotrexate there is thus a need for preparing the pure (6S) isomer either by resolving a suitable racemic mixture into its constituent isomers or by a stereospecific synthesis. In its application the Applicant has disclosed a process for the preparation of substantially pure 6R and 6S diastereoisomers of a derivative of tetrahydrofolic acid comprising the steps of (a) attaching a chiral auxiliary group at either N-5 or N-10 of a mixture of the 6R and 6S diastereoisomers of tetrahydrofolic acid or of a substituted tetrahydrofolic acid so as to form a pair of new diastereoisomers, (b) separating the pair of new diastereoisomers and (c) converting the substantially pure new diastereoisomers into the corresponding 6R and 6S isomers of the tetrahydrofolic acid derivatives. Using this process the Applicant has been able to produce the 6S diastereoisomer of leucovorin in a purity of greater than 90%.

In claiming its invention the Applicant included claims 1 to 12 directed to the new process itself and claims 13 to 27 directed to the substantially pure 6S and 6R diastereoisomers of derivatives of tetrahydrofolic acid including leucovorin, 5-methyl-, 5,10-methylene or 5,10-methylene-tetrahydrofolic acid and compositions containing them. In his Final Action the Examiner rejected claims 13 to 27 on the grounds that the compounds claimed therein were essentially disclosed in the prior art references. Claims 14, 22 and 25 which are representative of the rejected claims are as follows:

> 14 A substantially pure (6R or 6S) diastereoisomer of a derivative of tetrahydrofolic acid selected from leucovorin (5-formyltetrahydrofolic acid) or salt or ester thereof and 5-methyl- or 5,10 methylene- or 5,10-methenyl-tetrahydrofolic acid or salt or ester thereof which has a purity of greater than 75%
>
> 22 A composition for effecting methotrexate rescue in a mammal which comprises for administration to said mammal an effective amount of the substantially pure (6S) diastereoisomer of leucovorin according to claim 16 in a pharmaceutically acceptable carrier therefor
>
> 25 A substantially pure pharmaceutically acceptable compound which is a (6S) diastereoisomer selected from the group consisting of (6S) leucovorin (5-formyl-(6S)-tetrahydrofolic acid) and pharmaceutically acceptable salts and esters of (6S) leucovorin, wherein said substantially pure compound includes a mixture of (6S) and (6R) diastereoisomers and comprises at least 90% by weight of the (6S) diastereoisomer, the balance of said substantially pure compound being comprised of the (6R) diastereoisomer

In making this rejection the Examiner stated in his Final Action, in part, that:

The refusal of claims 13 to 27 is maintained Claims 1 to 12 are allowable

References Re-Applied.

Publications

Cancer Research 41, October, 1981, Straw et al
Cancer Research 44, July, 1984, Straw et al
Biochemical Pharmacology, Vol 28, Sirotnak et al
Chemistry and Biology of Pteridines, 1983, Rees et al
The Journal of Biological Chemistry, April 1963, Kaufman et al
Biochemical Pharmacology, Vol 31, No 8, 1982, Chello et al
Analytical Biochemistry, 122, 1982, Moran et al
Cancer Treatment Reports, 1981, Temple, Jr et al
JACS, 1952, Cosulich et al
Folates and Pterins, 1984, Blakely et al
JACS, 1979, Fontecilla-Camps et al

Reference Applied

Publication
Helvetica Chimica Acta, Vol 64, Fasc 8 (1981), Nr 266, pp 2627-35, Viscontini et al

The above cited art has disclosed various diastereoisomeric mixtures and pure diastereoisomers of the various tetrahydrofolic acid derivatives and their corresponding pharmaceutical utilities In order to be patentable a product must be new according to Section 2 of the Patent Act Moreover, if a product is not new according to Section 2 of the Act, it cannot form the basis of a process dependent claim even though the process itself may be new [Hoffmann-Laroche & Co Ltd v Commissioner of Patents (1954) Ex C R 52, (1955) S C R 414] Therefore, claims 13 to 18 and 22 to 27 are rejected, and claims 19 and 21 are rejected as being too broad as to include subject matter taught in the above art

Claims 13 to 27 are also rejected because the subject matter thereof lacks inventive ingenuity in view of the cited art, as the difference thereover is held to be obvious to one of ordinary skill in the art to which the alleged invention pertains Slight variations in the purity of the tetrahydrofolic acid derivatives would lead to predictable pharmaceutical results since both mixtures and pure diastereoisomers of said derivatives have already been taught in the prior art

In its response to the Final Action dated September 10, 1992 the Applicant submitted amended claims 13 to 23 to replace rejected claims 13 to 27 and asked that their allowability be considered. Claims 13, 18 and 21 which are representative of these amended claims are as follows:

13 A substantially pure (6S) diastereoisomer of leucovorin (5-formyltetrahydrofolic acid) or salt or ester thereof of purity greater than 90% when prepared by a process according to any one of claims 1 - 12

18 A substantially pure pharmaceutically acceptable compound which is a (6S) diastereoisomer selected from the group consisting of (6S) leucovorin (5-formyl-(6S)-tetrahydrofolic acid) and pharmaceutically acceptable salts and esters of (6S) leucovorin, wherein said substantially pure compound includes a mixture of (6S) and (6R) diastereoisomers and comprises at least 90% by weight of the (6S) diastereoisomer, the balance of said substantially pure compound being comprised of the (6R) diastereoisomer

21 A pharmaceutical composition for therapeutic use which comprises a substantially pure pharmaceutically acceptable compound which is a (6S) diastereoisomer selected from the group consisting of (6S) leucovorin (5-formyl-(6S)-tetrahydrofolic acid) and pharmaceutically acceptable salts and esters of (6S) leucovorin, wherein said substantially pure compound includes a mixture of (6S) and (6R) diastereoisomers and comprises greater than 90% by weight of the (6S) diastereoisomer, the balance of said substantially pure compound being comprised of the (6R) diastereoisomer, in combination with a pharmaceutically acceptable carrier

In assessing these amended claims the Board notes that amended claim 14 is clearly allowable since it is directed solely to intermediate compounds prepared by the exercise of the Applicant's process. It is also noted that the remaining claims have also been restricted to claiming the (6S) diastereoisomer of leucovorin in a purity greater than 90% and to compositions containing it. Since the claims no longer cover derivatives of 5-methyl-, 5,10-methylene or 5,10-methenyl-tetrahydrofolic acid those prior art references, notably Kaufman, Blakely and Viscontini, which relate to these derivatives are no longer pertinent. Furthermore the Board considers that the amended claims also meet the subsidiary objections made by the Examiner in his Final Action, for instance the objections to former claims 13 to 24 based on the grounds that these claims are essentially indefinite.

The remaining question before the Board is therefore whether or not the (6S) diastereoisomer of leucovorin having a purity of greater than 90% has been disclosed in any of the remaining prior art references cited by the Examiner.

The Board has carefully considered Applicant's discussion of each of the references and agrees that none of them clearly and unequivocally show the preparation of the (6S) diastereoisomer of leucovorin in a purity of greater than 90%. The most pertinent reference, Cosulich et al., purports to show the preparation of the diastereoisomers of leucovorin in what would be commercially useful quantities by a process involving the fractional crystallization of their calcium salts. However the Applicant has stated that attempts by other researchers to repeat the Cosulich process did not produce the desired optically pure diastereoisomers. Thus in U.S. patent number 5,010,194 to Eprova AG it is stated, at column 2, line 6, that:

> Several attempts have been made to resolve 5-CHO-(6R,S)-THF and to carry out the asymmetric synthesis of 5-CHO-(6S)-THF D Cosulich et al , J Amer Chem Soc 74, 4215-16, U S Pat No 2,688,018 (Aug 31, 1954) have attempted, for example, to bring about the resolution by fractional crystallization of an alkaline earth metal salt, for example, the calcium or strontium salt, of 5-CHO-(6R,S)-THF from aqueous solutions [see also J C Fontecilla-Camps et al , J Amer Chem Soc. 101, 6114 (1979)].

> However, the desired resolution cannot be achieved under the conditions published by D Cosulich et al On crystallization of, for example, the calcium salt of 5-CHO-(6R,S)-THF from water at Ph 7-8 it is always the 6R,S form which is recovered, as can be demonstrated quantitatively by means of chromatographic analysis on a chiral HPLC column and on the basis of the optical rotation

and further, at column 4, line 28, that:

> The often cited method of D Cosulich et al. could never by reproduced by subsequent scientists because, e g pure calcium (6S)-folinate is more soluble in water than calcium (6R)-folinate and calcium (6R,S)-folinate.

Furthermore the Applicant has stated that the author of the paper, Donna Cosulich, was and still is an employee of the American Cyanamid Company who have for many years sold racemic mixtures of leucovorin. The Applicant also states that it believes that American Cyanamid has also failed to reproduce Cosulich's work. American Cyanamid also is stated to have taken a licence under the Applicant's application implying that the company does not have a practical method of preparing the 6S diastereoisomer of its own. From this information it is clear to the Board that the Cosulich reference must, as the Applicant has indicated, be disregarded. As to the other references the Board is of the opinion that while some of them may disclose the preparation of the 6S diastereoisomer in very small amounts none of them show a product having the purity disclosed in the present application.

The Applicant has also provided a copy of a statutory declaration signed by co-inventor, Colin J. Suckling, stating, in part, that the invention provides 6S leucovorin in purities of at least 90% and that such high purities could not be attained prior to the present invention.

In view of this statutory declaration and in view of the Board's assessment of the cited references the Board recommends that claims 13 to 27 be replaced by amended claims 13 to 23 and that the application be returned to the Examiner for further prosecution consistent with the recommendation.

P.J. Davies
Chairman

M. Howarth
Member

I concur with the recommendation of the Board and return the application to the Examiner for further prosecution consistent with the Board's recommendation.

S. Batchelor
Commissioner of Patents

Dated at Hull, Quebec,
this 12 day of 12/96