COMMISSIONER'S DECISION

UNOBVIOUS (Section 45(4)): Advantage Over Prior Art.

A small quantum of invention may suffice for a patent. In a crowded art slight improvements may sustain a patent. It is often difficult to predicate results obtainable from chemical substances. Laevolysine is an essential element of animal diets, but dextro-lysine has no nutritional value. Held that the process of racemization of dextro-lysine to increase the presence of laevo-lysine by heating the sulphanite of d-lysine, sulphanilic acid being a weak acid, is not obvious from the prior racemization of optical isomers in the presence of strong acids and bases.

FINAL ACTION: Reversed.

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This decision relates to the rejection of claims in application 063891 during conflict proceedings. The application was filed on September 30, 1969 by Stamicarbon N.V., assignee of W. K. van der Linden et al, for an invention for a Process for the Preparation of a Salt of Optically Active Lysine, Class 260/238.16. The application was found to be in conflict with another copending application, and during re-examination at the Section 45(4) stage of the conflict proceedings, three claims were rejected as being unpatentable in view of certain prior art references. The rejection was referred to the Patent Appeal Board for review. Since the applicant did not request a hearing, the review is based upon the records on file.

The invention is for a process to convert optically active lysine sulphanilate into an optically inactive form (the racemate or DL form), which is a mixture of the two optically active forms of lysine. Lysine is an amino acid which occurs in nature as a constituent of proteins. The lysine which does occur naturally is the optically active laevo form (l-lysine) which is an essential component of animal diets. The other optical form, dextro-lysine (d-lysine) has no nutritional value. When lysine is made synthetically it is an optically inactive form consisting of a mixture of laevo and dextro lysine. It has now been found that the desirable L-form can be concentrated from the DL-mixture by converting the mixture into the sulphanilic acid salt, dissolving the salt, and selectively precipitating the L-lysine from the solution. This process is essentially the same as prior art processes in which other acids, such as 3,5-dinitrobenzoic acid, anthraquinone-β-sulphonic acid, 1-chloronaphthalene 4-sulphonic acid or β-napthalenesulphonic acid are used, but there are certain advantages in using sulphanilic acid (also called paraminobenzenesulphonic acid) in place of those acids. The Office considered those advantages

to be unobvious, and concluded during the conflict proceedings that that phase of the process is patentable.

A further embodiment of the invention involves heating the sulphanilate of one of the isomers, such as the d-lysine, in an inert solvent. This process racemates the d-lysine, i.e. it is converted into a mixture of d & l lysine. The racemate so produced can then be treated as described above to separate out the desired L-form. By this method it is possible to convert the d-form into the more desired l-form. It is this last embodiment which the applicant is now claiming, and which the examiner has held to be unpatentable.

The examiner applied the following references and found the invention to be unpatentable in view of them for the reasons stated below.

References Applied

United States Patents

2,586,154	Feb. 19, 1952	Cl. 260-534	Emmiek
3,213,106	Oct. 19, 1965	Cl. 260-319	Sasaji et al

Gilman: Organic Chemistry, Vol. 1, pages 176-181, (1938).
Wheland: Advanced Organic Chemistry, 2nd Edition, pages 250-261, (1951).
Wertheim: Textbook of Organic Chemistry, 2nd Edition, page 340, (1947)
Noller: Chemistry of Organic Compounds, pages 333-334, (1951).
Fieser and Fieser: Organic Chemistry, 2nd Edition, pages 272-274, (1950).

Conflicting claim C12 and claims 2 and 3 are rejected in view of the above cited references. These references describe the racemization of optically active organic compounds to produce the racemate mixture thereof by heating the optically active organic compounds in inert solvents; and in particular the racemization of optically active α-amino acids by heating to temperature between about 150° and 200°C in inert solvents. The process claimed in claim C12 (claim 1) and claims 2 and 3 fail to patentably distinguish over the cited references as the claims claim the racemization of optically active lysine sulphanilate by heating in an inert solvent.

The applicant argued on November 30, 1972 that the references were inapplicable for the following reasons:

> United States Specification 2,586,154 discloses that D-lysine (and of course also L-lysine, but this is not important in practice) can be racemised by heating it with hydrochloric acid (column 1, lines 51-52) or by heating either free D-lysine or D-lysine monohydrochloride in combination with phosphoric acid (column 2, lines 52-54).
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> United States Specification 3,213,106 discloses (column 2, lines 1-15) that D-lysine can be racemised in water, preferably in the presence of approximately equimolecular amounts of acid to avoid decomposition of the amino acid. In addition to hydrochloric acid other strong acids such as sulfuric acid, phosphoric acid, oxalic acid, trichloroacetic acid and the like are also effective in equivalent amounts.
>
> The cited textbooks disclose only general considerations in respect of racemisation and are less relevant than the above mentioned United States Specifications.
>
> In the racemisation process as claimed in the present application D-lysine is racemised in the presence of an equimolecular amount of sulphanilic acid (which is in fact an internal salt having weaker acidic properties than the strong acids mentioned in United States Specification 3,213,106). There is thus prepared, without any perceptible decomposition, a DL-lysine-salt having a special property, namely, that it can be optically resolved by the method of selective crystallization.
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> At the priority date of the present application there were only four DL-lysine salts known with the same property as DL-lysinesulphanilate. These salts are mentioned in the Dutch patent application 6,711,971 published 1st March 1968 (The United States Specification 3,527,776 corresponds with this publication) and are discussed in the present application at page 2, paragraph 2. Three of the said known DL-salts are less suitable for the selective crystallization because of the low yield and low optical purity of the crystallized salt. The fourth salt (the salt of DL-lysine with 3,5 dinitrobenzoic acid) is more suitable for the selective crystallization. However, this DL-salt cannot be prepared by racemization of the corresponding D-lysine-salt because a strong decomposition takes place (see lines 14-16, page 2 of the description). Whether or not, the other three known DL-salts can be prepared by the racemisation process as claimed has not been tested.
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> In the cited references, nothing is disclosed in respect of the preparation of a DL-lysine salt having the above-mentioned special property. The salts of DL-lysine and the strong acids mentioned in United States Specification 3,213,106 do not have such property. The relevant art in this connection is the said Dutch application 6,711,971. However, not just any DL-lysine salt with the said property can be prepared according to the claimed racemisation method and not just any acid is in general suitable in the racemisation of D-lysine.
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> The preparation of DL-lysinesulphanilate by racemisation of D-lylinesulphanilate is consequently a new and unobvious process, because of first the new and unobvious property of the DL-salt prepared. Secondly, because sulphanilic acid is an internal salt with weak acidic properties and the use of such an 'acid' is unobvious in view of United States Specification 3,213,106. Thirdly, the known other DL-lysine salt having the same property (salt with 3,5-dinitrobenzoic acid) cannot be prepared by the same method.

In a latter response, on June 11, 1973, he added the following comments:

> (1) D-lysine could be racemized without any perceptible decomposition by heating an aqueous solution of D-lysine in the presence of an equimolecular amount of a strong acid (U.S. spec. 3,213,106).
>
> (2) Four salts of DL-lysine with an optically inactive acid could be optically resolved by the method of selective crystallization (U.S. spec. 3,527,776 corresponding with Dutch spec. 6,711,971).
>
> At the priority date of the present application it was not known that by heating an aqueous solution of D-lysine in the presence of an equimolecular amount of sulphanilic acid, being an internal salt with weak acidic properties, a salt of DL-lysine could be prepared without any perceptible decomposition and having the same property as the four known DL-lysine salts mentioned in U.S. spec. 3,527,776.
>
> To demonstrate the unobviousness of the claimed process, we enclose results of comparative experiments. These experiments relate to the racemization of D-lysine-sulphanilate and of the salt of D-lysine with 3,5-dinitrobenzoate acid. The DL-lysine salt of this acid is the most suitable salt in respect of the selective crystallization which was known at the priority date of the present application.

What the Board must do is analyse the prior art, which discloses closely related inventions, to determine whether such differences as do exist suffice for a holding that the new process would have been unobvious to a skilled chemist when the application was filed.

Racemization of optical isomers, as shown in by the text book references cited by the examiner, is well known. Racemization of lysine itself was also known in the presence of strong acids and bases. Heretofore, however, no one had prepared the sulphanilic acid salts of lysine, nor racemized that salt. It was the position of the examiner that because of the prior art it would have been obvious to racemize the sulphanilic acid in order to increase the production of L-lysine, and equally it would have also been evident that the process would work. While there is some justification for such a conclusion, we have reservations about coming to it. The prior art racemizations of lysine were done

in the presence of strong acids, such as hydrochloric and trichloracetic acids. Sulphanilic acids, by contrast is an internal salt having relatively weakly acidic properties. At the priority date of the application only four salts of lysine were known to be useful for selective crystallization of lysine, and attempts to racemate at least one of those led to considerably more decomposition than when lysine sulphanilate is used. Consequently we have come to the conclusion that there is a reasonable doubt that the racemization being claimed would have been obvious, or that the Commissioner could be satisfied within the meaning of Section 42 that the applicant is not entitled to a patent.

Admittedly the quantum of invention present is small, but if any is present, that will suffice for a patent. This is a crowded art, where slight improvements might sustain a patent. The Office's previous conclusions that the separation of lysines using sulphanilic acid itself is patentable is testimony to that. It is also supported by a long line of judicial decisions. See, for example, Jamb Sets v Carlton 1964 Ex. C.R. 377, Scragg & Sons v. Leesona, 1964 Ex. C.R. 649 or Wright & Carson v Brake Service 1925 Ex. C.R. 127 at 131. Furthermore, as was observed by Maclean, J. in Chipman Chemists v. Fairview Chemical 1932 Ex. C.R. 107 it is often difficult to predicate the results that may be obtained from chemical substances:

> ... Where chemical action is involved analogy does not carry one far...

We have reached the conclusion that in this instance there may well be invention present, and that the application should be allowed to proceed.

There is one other matter for consideration. The applicant has proposed an amendment to claim C12 which relates the racemization process to the selective crystallization process. Whether this alteration is made or not is immaterial to the conclusion we have reached, and should be left for the consideration of the examiner during subsequent prosecution.

Gordon Asher,
Chairman,
Patent Appeal Board.

I concur with the findings of the Patent Appeal Board. The rejection is to be withdrawn, and prosecution resumed.

Decision accordingly,

A.M. Laidlaw,
Commissioner of Patents.

Dated at Hull, Quebec,
this 9th. day of
September, 1974.

Agent for Applicant

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