

UNITED STATES PATENT OFFICE

2,536,360

RACEMIZATION OF LYSINE

Robert D. Emmick and Kenneth O. Hambrook,
Niagara Falls, and Arthur O. Rogers, Lewiston,
N. Y., assignors to E. I. du Pont de Nemours &
Company, Wilmington, Del., a corporation of
Delaware

No Drawing. Application November 25, 1949,
Serial No. 129,596

9 Claims. (Cl. 260-534)

1

This invention relates to the racemization of amino acids and more particularly it relates to a novel process for the racemization of lysine.

Lysine is one of the amino acids which occur in nature as constituents of proteins. The lysine which occurs naturally is optically active, its aqueous solutions rotating the plane of polarized light to the right and this form is commonly designated as l(+)-lysine. In this form lysine is an essential component of animal diets whereas the enantiomorphous d(-)-lysine has no known nutritional value.

Lysine which has been synthesized from optically inactive materials, for example, by the process of Eck and Marvel, Organic Syntheses Collective Vol. II, page 374, or by the process described in application S. N. 70,799 filed January 13, 1949 is optically inactive and consists of equal parts of the biologically active l(+)-isomer and the biologically inactive d(-)-isomer. Thus, its nutritional value can be doubled by converting its d(-)-lysine content into the l(+)-form while retaining the quantity of the latter initially present.

It is possible to convert synthetic lysine completely to the biologically active form by first separating the isomers (resolution) and then converting the inactive d(-)-lysine back to the dl-mixture (racemization). By a repetition of these operations, the lysine is eventually converted entirely into the l(+)-form. As a practical matter, it is unnecessary and usually impossible to effect a complete separation of the l(+)-lysine and the d(-)-isomer. The requirements for an economically feasible process are that a substantial portion of the l(+)-lysine be isolated in pure form in the resolution step and that no serious loss of total lysine occur in either step.

Resolution of dl-lysine is usually effected by combining the material to be resolved with an optically active compound known as the resolving agent and fractionally crystallizing the product. This may be accomplished by known methods. For example, in a method disclosed by C. P. Berg in the Journal of Biological Chemistry, vol. 115, pages 9-15, 1936, d-camphoric acid is used as a resolving agent to obtain l(+)-lysine. This author also shows the use of l-camphoric acid to obtain d(-)-lysine.

The racemization of lysine, or conversion of the optically active material to the racemic mixtures, has previously been accomplished by heating the isomer with hydrochloric acid. This method is disclosed in Ber. 35, 3778, (1902).

2

Although good recoveries of lysine are obtainable by this method, the mixture of hydrochloric acid and lysine is highly corrosive to metals, particularly at the temperatures necessary to effect racemization at a practical rate. Thus, expensive corrosion resistant equipment is necessary if this method is to be used. Attempts to use this method by reducing the proportion of hydrochloric acid to that stoichiometrically equivalent to the lysine present have failed to obviate this serious disadvantage. The use of hydrochloric acid also results in a complicated process since it is first necessary to replace the resolving agent with the hydrochloric acid prior to racemization and following the racemization step it is necessary to reconvert the lysine to the free form before it can be recombined with the resolving agent in the next operation. Another method for the racemization of lysine which is disclosed in U. S. P. 2,071,327 consists in heating the amino acid with acetyl chloride in the presence of acetic acid. Obviously, this method is even less desirable than the one described above.

It is an object of this invention to provide a simple, practical and economical process for the racemization of lysine. Another object is to provide a process for the racemization of lysine wherein the operation may be carried out under non-corrosive conditions permitting the use of ordinary metal equipment. A further object is to provide a new and improved process by which a mixture of l(+) and d(-)-isomers of lysine may easily be recovered from the reaction medium. Still another object of the invention is to provide a new process wherein a mixture of l(+) and d(-)-isomers of lysine may be resolved, the undesired isomer racemized in accordance with the process described herein and the resulting mixture recycled direct to the resolution step. These and other objects will be apparent from the ensuing description of the invention.

The above objects are attained in accordance with this invention by heating optically active lysine in combination with a cation-exchange material.

In a preferred mode of operating the invention, an optically active lysine is heated in combination with a cation-exchange material in the presence of water.

In general, the process of this invention is carried out by passing an aqueous solution of optically active lysine which may be in the form of free lysine, a salt of lysine with a resolving agent, or other suitable form into a cation-exchange material and heating to the desired tem-

3

perature until racemization is accomplished. The time required for complete racemization will vary with the temperature as well as the ratio of optical isomers in the lysine treated and usually a few minutes to 48 hours is sufficient. It is preferred to carry out the racemization by operating within the range 100° C. to 230° C. A temperature of 150° C. has been found entirely satisfactory. Although higher temperatures may be utilized if desired, relatively heavy equipment is necessary to withstand the pressure developed and some decomposition of lysine and the cation-exchange material may occur. Temperatures below 100° C. may be utilized, but the reaction is slow and therefore requires larger reaction vessels for a given production rate.

Although racemization may be carried to completion in accordance with this invention it is unnecessary and may be undesirable in practical operation to racemize completely. Since mixtures containing varying proportions of l(+)-lysine and d(-)-lysine may be resolved without difficulty it is entirely satisfactory to stop the racemization at any desired point. However, it is of course desirable to increase substantially the proportion of the desired isomer in the mixture.

Although lysine may be racemized by heating in combination with the cation-exchange material in the absence of water, it is preferred to operate in the presence of water to avoid loss of lysine through dehydration reactions.

Any of the well-known cation-exchange materials may be utilized in the practice of this invention. As commonly used the term cation-exchange materials refers to a class of insoluble polymeric materials which contain acidic groups capable of combining with a variety of cations to form insoluble salts. A typical example of a cation-exchange material is described in U. S. P. 2,366,007. Other examples include polyphenol-sulfonic acids, sulfonated hydrocarbon polymers and polycarboxylic acids. Sulfonated coals and natural and synthetic zeolites having cation-exchange properties are also suitable in the practice of this invention. The selection of a particular cation-exchange material will depend upon such considerations as capacity, exchange rate, mechanical ruggedness and chemical stability as well as cost. Any of the commercially available cation-exchange materials are suitable in the practice of this invention. For example, satisfactory results have been obtained with cation-exchange materials sold under the names "Dowex-50," "Amberlite IR-100," "Amberlite IR-105," "Amberlite IR-120," "Ionac C-200," "Duo-lite C-3," "Amberlite IRC-50" and "Permutit Q."

A preferred class of cation-exchange materials are those in which the acidic groups are sulfonic acid groups as exemplified by the sulfonated hydrocarbon polymers. These cation-exchange materials are particularly valuable in the practice of this invention since they possess excellent chemical and physical stability under the conditions utilized, are readily available, and have high capacity and exchange rate.

The following examples are illustrative of the invention.

Example 1

One-half mole (246 g.) of lysine d-camphorate in which the ratio of d(-)-lysine to l(+)-lysine was 64:36 was passed through a 1.5-liter bed of a commercial cation-exchange resin comprising a sulphonated polymerizate of a polyvinyl aryl

4

compound in its ammonium form. After washing, the resin-lysine combination was heated for 18 hours at 149° C. in a pressure-tight vessel. The resin was eluted with 10% ammonia and the effluent boiled to expel the excess ammonia. Free lysine recovered was equivalent to 89% of that originally fed to the resin bed and to virtually all of that retained by the resin during the charging operation. The ratio of d(-)-lysine to l(+)-lysine in the product was 52:48.

Example 2

The following table shows the effects of time and temperature on the racemization of lysine in combination with the cation-exchange material used in Example 1. The experimental procedures were similar to that described in Example 1.

L(+)-Lysine before treatment	Heating Time, Hrs.	Temperature, °C.	L(+)-Lysine after treatment, per cent
32	16	130	41
32	40	130	46
36	18	149	48
33.1	0.5	190-197	49

¹ 50% l(+)-lysine content corresponds to complete racemization.

Example 3

The effectiveness of representative cation-exchange resins in promoting the racemization of lysine was tested in the following experiment. In each case 50 cc. of the resin in ammonium form was charged with 200 cc. of a solution containing lysine combined with resolving agent, in which the ratio of l(+)-lysine to d(-)-lysine was 18.5:81.5. After washing, the charged resins were sealed in glass pressure tubes and heated 16 hours at 150° C. The lysine from each was then eluted with 10% ammonia, the excess ammonia boiled off and the percentage of l(+)-lysine in the recovered material determined. It should be noted that capacities and optimum flow rates for the different resins were not determined, and hence that the recoveries of lysine were incomplete in most cases.

Cation-exchange Material ²	Lysine content of Charging Solution	Lysine Recovered	
		Per Cent of charge	l(+)-Content ¹
	G.		Per cent
A	4.10	63	47
B	4.10	75	50
C	3.69	100	50
D	4.10	68	47-50
E	4.10	74	50
F	4.10	47	50

¹ 50% l(+)-content indicates complete racemization.

² In this case the lysine was recovered partially as free lysine and partially as lysine dihydrochloride.

³ Six different commercially available cation-exchange materials.

Example 4

Two hundred forty-six grams of lysine d-camphorate in which the ratio of d(-)-lysine to l(+)-lysine was 64:36 was dissolved in 1 gallon of water and passed slowly through a bed of cation-exchange resin in ammonium form. The resin was washed with water until free of ammonium camphorate and camphoric acid recovered in 96% yield from the effluent and washings. The cation-exchange resin was transferred to a glass-lined steel pressure vessel and heated at approximately 140-150° C. in the presence of wa-

5

ter for seventeen hours. After cooling the resin was removed from the pressure vessel and eluted with 3 liters of 10% ammonia. The elutriate was evaporated and the recovery of lysine found to be 89.4% of theoretical. The ratio of 1(+)-lysine to d(-)-lysine in the product was 48:52. The product was combined with 89 g. of d-camphoric acid and resolved by fractional crystallization from 50% aqueous methanol. The crystals thus obtained weighed 54.3 g., representing a 52% yield of 1(+)-lysine d-camphorate; the optical purity of the product was 94%.

Although the process of this invention is useful in racemizing optically active lysine from any source, it is of particular utility as a part of the resolution-racemization cycle involved in converting dl-lysine or other mixture of 1(+) and d(-)-lysine to a pure optical isomer. This procedure which may vary in detail consists essentially in resolving lysine by known methods, for example, the method described by Berg, separating the desired isomer, heating the remaining undesired isomer in contact with the cation-exchange material to effect racemization, recovering a mixture of 1(+) and d(-)-lysine and returning the latter to the resolution step. An example of this mode of operation follows.

A mixture of 1(+) and d(-)-lysine is resolved with d-camphoric acid and the 1(+)-isomer is crystallized out and separated from the mother liquor. The mother liquor may contain water, methanol and salts of the resolving agent with lysine in which the d(-)-isomer of the latter predominates. The mother liquor is diluted with water and passed through a bed of cation-exchange material preferably in the ammonium form. During this passage and subsequent washing with water, the camphoric acid passes into the effluent in combination with ammonia and may be recovered for reuse. The d(-)-lysine is held in combination with the cation-exchange material. The cation-exchange material with the combined lysine is then heated at the desired temperature in the presence of water to racemize the lysine. The cation-exchange material is then eluted with aqueous ammonia which displaces the lysine and reconverts the cation-exchange material to its ammonium form. The effluent containing ammonia and lysine is partially evaporated to remove ammonia and the residual solution of a mixture of 1(+) and d(-)-lysine is returned to the resolution step.

In the process described above it is preferred to utilize the cation-exchange material initially in its ammonium form or other form capable of producing soluble salts of the resolving agent. Otherwise, difficulty may be encountered in washing the resolving agent completely from the cation-exchange material. If desired, the amine,

6

sodium or other form of the cation-exchange material which will yield soluble salts with the resolving agent may be utilized.

The process of the present invention provides a simple and efficient process for the racemization of lysine and is especially suitable for large scale commercial operation. It is particularly valuable in connection with recently developed methods for the production of synthetic lysine which is potentially of major importance as a component of animal feed.

We claim:

1. Process for the racemization of lysine which comprises heating optically active lysine in combination with a cation-exchange material.
2. Process for the racemization of lysine which comprises heating optically active lysine in combination with a cation-exchange material in the presence of water.
3. The process of claim 2 wherein the temperature is maintained at 100-230° C.
4. The process of claim 3 wherein the acidic groups of the cation-exchange material are sulfonic acid groups.
5. Process which comprises resolving a mixture of 1(+) and d(-)-lysine, separating a desired optically active isomer, heating the remaining undesired optically active isomer in combination with a cation-exchange material and recovering a mixture of 1(+) and d(-)-lysine.
6. Process which comprises resolving a mixture of 1(+) and d(-)-lysine into 1(+)-lysine and d(-)-lysine, separating 1(+)-lysine, passing an aqueous solution of the remaining d(-)-lysine into contact with a cation-exchange material, heating said d(-)-lysine in combination with said material in the presence of water and recovering a mixture of 1(+) and d(-)-lysine.
7. The process of claim 6 wherein the acidic groups of the cation-exchange material are sulfonic acid groups.
8. The process of claim 6 wherein the cation-exchange material is initially in the ammonium form.
9. Process which comprises resolving a mixture of 1(+)-lysine and d(-)-lysine, separating 1(+)-lysine, passing the mother liquor from the resolution step into a cation-exchange material, recovering resolving agent from the effluent, heating said cation-exchange material in combination with lysine containing predominant amounts of d(-)-lysine whereby said lysine is racemized, eluting said cation-exchange material with ammonia, and recovering a mixture of 1(+) and d(-)-lysine from the elutriate.

ROBERT D. EMMICK.
KENNETH O. HAMBROCK.
ARTHUR O. ROGERS.

No references cited.