CALCIUM PANTOTHENATE FROM JAPAN

Report on Preliminary Investigation
No. 603-TA-5 Under Section 603
of the Trade Act of 1974

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UNITED STATES INTERNATIONAL TRADE COMMISSION

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Introduction

On February 20, 1980, the Commission issued a notice of preliminary investigation under section 603 of the Trade Act of 1974 (19 U.S.C. 2482) to investigate whether imports of calcium pantothenate from Japan are the subject of a combination, contract, or conspiracy to restrain trade and commerce in the United States, or the subject of a scheme to monopolize the d-calcium pantothenate (d-cal pan) and or dl-calcium pantothenate (dl-cal pan) markets in the United States. The preliminary investigation was undertaken by the Commission after dismissal of a section 337 complaint filed on October 24, 1979, by Syntex Agribusiness, Inc. (Docket No. 604), alleging unfair methods of competition and unfair acts in the importation and sale of calcium pantothenate from Japan. 1/

On February 12, 1980, the Commission voted to dismiss the complaint filed on October 24, 1979, by Syntex Agribusiness, Inc. The Commission had found that Syntex' complaint was not properly filed under rule 210.12. This decision was based on section 337(b)(3) of the Tariff Act of 1930, as amended by section 1105 of the Trade Agreements Act of 1979, which gives the Commission discretion regarding the institution of investigations when the Commission has reason to believe the matter before it is based in part on alleged acts and effects which are within the purview of the antidumping laws and in part on alleged acts and effects which may, independently from or in conjunction with those within the purview of such section, establish a basis for relief under section 337. The Syntex complaint alleged, among other things, predatory pricing, monopolization, and conspiracy to predatorily price and monopolize. Alleged conspirators were Alps Pharmaceutical and Mitsui & Co. The Commission's decision to dismiss the complaint was supported by the total lack of information that might give the Commission a reasonable indication that unfair trade practices within the Commission's jurisdiction might exist.

Nevertheless, the Commission did choose to institute a preliminary investigation under section 603 of the Trade Act of 1974 (19 U.S.C. 2482) to investigate certain aspects of the calcium pantothenate market in the United States and to see whether Syntex' charges might merit a section 337 investigation, in spite of the paucity of hard information in the complaint.

1/ Syntex had filed an earlier sec. 337 complaint with the Commission on June 11, 1979 (Docket No. 579), containing essentially the same allegations as those contained its complaint filed on Oct. 26, 1979. The Commission had dismissed the earlier complaint, inasmuch as it was not considered to be properly filed under the Commission's Rules of Practice and Procedure.

The staff was instructed to address, among other issues, the following questions in the preliminary investigation:

(1) The identities of any and all participants in the d-cal pan and dl-cal pan markets in the United States and their respective market shares;

(2) The relationship among certain Japanese manufacturers or importers of calcium pantothenate;

(3) Any attempts by certain Japanese manufacturers or importers to absorb the amount of any antidumping duties imposed on these imported products;

(4) Prices charged by the certain Japanese manufacturers to U.S. importers and prices charged by U.S. importers to U.S. consumers for calcium pantothenate; and

(5) Cost of production for calcium pantothenate manufactured in Japan.

On June 19, 1980, the staff submitted a preliminary report on this investigation to the Commission. Shortly thereafter, the United States Court of Customs and Patent Appeals denied Syntex's petition in the nature of mandamus to compel the Commission to institute a section 337 investigation.

The staff conducted its investigation through interviews with representatives of the producers, importers, and users of cal pan, and through analyses of documents and other information furnished by these concerns. The staff also consulted import data which was furnished by the U.S. Customs Service. This report contains the final findings of the staff in this preliminary investigation.

Conclusions and recommendation

On the basis of the preliminary investigation undertaken by the staff, it is submitted that there are no unfair methods of competition and unfair acts in the importation and sale of cal pan by Mitsui & Co., Alps Pharmaceutical, or other companies, the effect or tendency of which is to destroy or substantially injure an industry efficiently and economically operated, in the United States, or to prevent the establishment of such an industry, or to restrain or monopolize trade and commerce in the United States.

Specifically, the conclusions drawn from this report are that:

(1) There is no evidence of any conspiracy between Mitsui and Alps (or others) involving imports of cal pan;

(2) There is no evidence of any predatory pricing schemes involving imports of cal pan;

(3) The evidence shows that sales of imported Japanese cal pan are occurring at competitive prices;

(4) The evidence shows that new domestic entrants in the d-cal pan submarket are rapidly eroding the dominance of Japanese suppliers in this submarket to the extent that no firm will be in a monopoly position in the d-cal pan submarket in the very near future; and

(5) The evidence shows that no firm has engaged in conduct which would be indicative of an attempt to monopolize the dl-cal pan submarket.

Accordingly, there is no basis for further investigatory activity, and it is recommended that the section 603 investigation be terminated and that the Commission not reconsider its vote not to institute a section 337 investigation on the basis of the matters alleged in the Syntex complaint.

I. Description and uses of calcium pantothenate

Calcium pantothenate (cal pan) is the calcium salt of pantothenic acid, one of the essential B vitamins. Like all essential vitamins, pantothenic acid (or cal pan which is converted to pantothenic acid when ingested by humans or animals) is required in minute amounts in the diets of humans and animals to maintain health and normal growth.

Pantothenic acid occurs in most foods consumed by humans, and deficiencies in humans are slow to develop, even when a semisynthetic diet is fed for several months. An experimental group of people were deliberately treated to induce a deficiency in pantothenic acid in order to observe the symptoms in humans. Complaints of fatigue, abdominal stress, and sleep disturbance were accompanied by headaches, malaise, nausea, and occasional vomiting. Flatulence and abdominal cramping, tingling of the hands and feet, cramping of the muscles of the leg, and an impairment of motor coordination were observed. Pantothenic acid deficiencies are unusual in humans who have a well balanced diet, but deficiencies are sometimes observed in individuals (some alcoholics for example) who have been subsisting on low quality diets. Usual adult requirements for pantothenic acid ranges from 5 to 20 mg. per day. Most multivitamin formulations (especially the widely promoted "stress" formulations) contain cal pan.

In contrast to human nutrition products, the large-scale production of caged or penned nonruminant animals, such as poultry and swine, requires the routine addition of cal pan (along with other vitamins) to the animal feed. Again, pantothenic acid provided by the cal pan is required in minute amounts but is essential for animal health and growth. Poultry with insufficient pantothenic acid in their diets develop dermatitis with skin lesions and grow at a reduced rate. The need of swine for pantothenic acid was not recognized until its use in poultry was well established. Pantothenic acid deficiencies in swine result in animals developing scabby dermatitis, symptoms of neurological degeneration, bronchial pneumonia, intestinal distention, and degeneration of liver function.

Poultry require from 2 to 11 mg. of pantothenic acid per kg. of feed, depending on the type of poultry operation. Growing chickens, for example, require 10 mg. of pantothenic acid per kg. of feed, while laying hens only require 2.2 mg. of pantothenic acid per kg. of feed. Swine require from 11 to 13 mg. of pantothenic acid per kg. of feed. One unit of pantothenic acid is equivalent to 1.087 units of cal pan, so a typical swine feed would only contain about 12 grams of cal pan in a ton of feed, but these amounts are often increased to 20 grams per ton of feed for increased nutritional value.

Pantothenic acid is an unstable, extremely hygroscopic (moisture retentive), viscous, and oily liquid. These objectionable properties of the acid have resulted in the calcium salt becoming the product of commerce. Human and animal metabolisms convert cal pan, when ingested, into pantothenic acid.

A rudimentary understanding of optical isomers and stereoisomers is essential in order to grasp the significance of the competitive relationships of the different cal pan products. Stereoisomers are chemicals that differ from one another only in the way the atoms or groups of atoms of the chemical molecule are arranged in space. Stereoisomers are called optically active because if polarized light is passed through a medium containing one type of stereoisomer, the plane of polarization is rotated. If the isomer rotates the polarized light to the right it is known as dextrorotatory (d), while if the polarized light is rotated to the left the isomer is called levorotatory (l). If the d and the l isomers are mixed in equal portions, then the mixture is not optically active and the mixture is called racemic (dl). In medicinal chemistry, frequently one stereoisomer is physiologically active while the other isomer may be inactive or have substantially different physiological properties.

Pantothenic acid and cal pan are optically active, but only d-pantothenic acid and d-cal pan have biological activity as a vitamin. The l-pantothenic acid and l-cal pan are physiologically inactive. A racemic mixture is 50 percent d and 50 percent l, is not optically active, and it is designated as dl-pantothenic acid or dl-cal pan. As mentioned before, only the calcium salt is an item of commerce, but it will often be marketed on a basis of pantothenic acid equivalent.

In the trade, consumers of cal pan purchase the material on the basis of vitamin activity calculated on the d-cal pan content or on the basis of how much d-pantothenic acid the product is equivalent to. Price per unit of activity is often a deciding factor, while other factors such as physical properties, quality, vendor service, packaging, product promotion, sales effort, and other factors also influence consumer preferences.

The most concentrated commercially available product is d-cal pan, 96-98 percent pure. It is marketed as an odorless white powder or crystal that is slightly hygroscopic. The d-cal pan is offered in a United States Pharmacopeia (U.S.P.) grade for use in human vitamin supplements and multivitamin capsules, and in an animal feed grade to supply the animal feed industry.

Racemic (dl) cal pan is a mixture of equal amounts of d-cal pan and l-cal pan and, therefore, has half of the vitamin activity of pure d-cal pan. The dl-cal pan is marketed as an odorless white powder that is more hygroscopic than pure d-cal pan. A U.S.P. grade has been marketed, but d-cal pan is the preferred product in the U.S.P. market, and domestic production of U.S.P. dl-cal pan has been discontinued. An animal feed grade dl-cal pan which contains 45 to 46 percent d-cal pan is presently produced and marketed in the United States.

Another article of domestic commerce is a mixture of dl-cal pan and calcium chloride which is said to form a "complex." This material is standardized to contain 320 grams of dl-cal pan (160 grams of d-cal pan) per pound of product. This product contains about 35 percent physiologically active material. The dl-cal pan-calcium chloride complex is not as hygroscopic as dl-cal pan alone, and remains free flowing under usual conditions of storage. This product is used in the animal feed market.

Dilutions of pure d-cal pan, dl-cal pan, and calcium chloride complex are made with a suitable inert carrier such as rice hulls or ground corn cobs to meet the needs of some animal feed mills that require a lower initial concentration of vitamin activity than provided by the more concentrated products.

II. Production processes

The basic chemistry for producing pantothenic acid and cal pan synthetically was developed in the mid-1940's and is still in use today.

In brief, synthetic pantothenic acid is made by the reaction of beta-alanine with pantolactone. Beta-alanine can be made in several ways, but the method most widely used is by the reaction of acrylonitrile with ammonia. Pantolactone is synthesized from formaldehyde and isobutyraldehyde. To produce cal pan the reactions are carried out in the presence of calcium ion, and the calcium salt is then produced. 1/

The usual synthesis yields dl-cal pan. Half of the raw materials are consumed in producing d-cal pan and the other half in producing the physiologically inactive, and hence worthless as a vitamin, l-cal pan.

Obviously, if some process were developed that would yield only d-cal pan utilizing all of the raw materials to produce the active isomer, then such a process would have a competitive advantage over the process which produces the racemic mixture. To a significant extent, the Japanese developed and patented processes during the 1960's and early 1970's which produce only d-cal pan as a final product and, thus, have (at least in theory) a cost-competitive advantage in producing this vitamin. In addition, an East German company has developed and patented a process (the "Jenapharm" process) 2/ to produce d-cal pan that is similar in some respects to the Japanese processes.

These relatively new processes generally do not alter the basic chemical reactions of the synthesis, but separate the d-isomer from the l-isomer and then recycle the l-isomer to produce more of the d-isomer. The relatively new resolution processes 3/ differ in details, but are all based upon a discovery that the pure d-isomer of cal pan or of various pantolates can be preferentially crystallized from a supersaturated solution rich in the d-isomer by seeding the solution with crystals of the pure d-isomer. The same is true for the l-isomer. For example, when a supersaturated solution with an excess of d-cal pan is seeded with pure d-cal pan crystals, additional pure d-cal pan will crystalize from the solution and can be removed and dried for sale. This leaves a solution with an excess of l-cal pan. When a supersaturated rich in l-cal pan is seeded with pure l-cal pan, additional pure l-cal pan will crystalize from the solution, leaving the solution with an excess of d-cal pan. The separated l-cal pan is converted into a racemic mixture, dl-cal pan, which is then recycled through the resolution process.

These new resolution processes 4/ to produce pure d-cal pan are not 100 percent efficient, and there are product losses and costs associated with the resolution steps. Nevertheless, the processes are currently used successfully in Japan and have been adopted in the design of two new large domestic plants.

1/ See exhibit A.
2/ See patents in exhibit B.
3/ Discussed in sections B and C.
4/ Ibid.

The Commission staff visited all of the three domestic plants producing cal pan, and a more detailed discussion of the production processes follows. Copies of relevant patents are included in exhibit B.

A. Synthesis of dl-cal pan at the Syntex plant [1]

Cal pan is the calcium salt of pantothenic acid [2] produced by the reaction of pantolactone with beta-alanine. Syntex reacts isobutyraldehyde with formaldehyde to obtain alpha, alpha-dimethyl-beta-hydroxy-propionaldehyde, which is then condensed with hydrocyanic acid in the presence of calcium chloride to produce dl-pantolactone. Syntex purchases beta-alanine (imported from Japan) to react with the pantolactone, in the presence of the calcium ion, to form cal pan.

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[1] See exhibit A.

[2] Pantothenic acid is optically active and exists as the "d" and the "l" isomers (calcium salt). Therefore, the d-cal pan is an abbreviation for the term dextrorotary, which means that a beam of incident polarized light is optically rotated to the right. The "l" in dl-cal pan stands for levorotary, which is the converse of dextrorotary in that the incident polarized light is rotated to the left. Racemization of cal pan involves the formulation of a chemical compound which contains equal quantities of dextrorotary and levorotary isomers so that it does not rotate the plane of incident polarized light. This apparently creates a more stable chemical compound having advantages in handling, storage, and use.

* * * * * * *

Several years ago Syntex produced beta-alanine as follows:

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At that time, the staff was informed, 1/ Syntex had a very cost-competitive synthesis for beta alanine. Beta-propiolactone, however, was found to be a patent carcinogen, and Celanese Corp., a company that was supplying this material to Syntex, stopped production in the early or mid-1970's, after which Syntex started purchasing beta-alanine. According to Syntex, the Japanese have a process to produce beta-alanine by reacting acrylonitrile with ammonia to form acrylic acid.

The synthesis reactions used by Syntex to produce and separate pantolactone utilize corrosive and toxic materials, and depending on the synthesis, must be carried out in glass-lined reaction and separation vessels or, for some stages of the process, stainless steel vessels. * * *

The reaction process used by Syntex yields a mixture of dl-cal pan. At one time, Syntex separated some of the material and isolated the d-cal pan which is the only isomer with physiological activity. Syntex, however, alleges that it stopped production of d-cal pan in 1976 because they were not price competitive with imports from Japan. 2/ * * *

1/ Mar. 21, 1980, interview with Syntex officials in Springfield, Mo.
2/ Ibid. See also Syntex' sec. 337 complaint.

Up until 1979, Syntex produced a medicinal grade of dl-cal pan which required additional purification steps not required for the animal-feed grade material. Since d-cal pan is the preferred material for use in human vitamin formulations, Syntex discontinued production of the medicinal grade dl-cal pan, and, again, it is unlikely that they will reenter this market owing to the price of Japanese d-cal pan. 1/

Presently, Syntex produces and sells only animal-feed grade dl-cal pan and a calcium chloride complex. The dl-cal pan is highly hygroscopic, which presents some handling and storage problems. The dl-cal pan - calcium chloride complex is non-hygroscopic and remains a free-flowing product under normal conditions. Syntex offers several standard dilutions of the dl-cal pan - calcium chloride complex which they call "Pantoplex" 160, 96, 80, 64, 32. Pantoplex 160 contains 160 grams of d-cal pan per pound, Pantoplex 96 contains 96 grams of d-cal pan per pound, etc. Syntex claims 2/ that many feed mills prefer their Pantoplex products, as the mills get a more uniform feed mixture than they would if they used pure d-cal pan. According to Syntex, there are no known imports of dl-cal pan - calcium chloride complex. Syntex is primarily being harmed by imports of dl-cal pan (rather than by imports of d-cal pan). 3/

B. Synthesis of d-cal pan at the Diamond Shamrock Corp. plant 4/

Diamond Shamrock's new cal pan plant is located on a 20-acre site adjacent to its animal-feed premix plant in Van Buren, Ark. The cal pan plant is large for a vitamin plant, and when fully operational will have an annual capacity of 725 metric tons of d-cal pan. It is a "world scale" plant in that Diamond Shamrock

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1/ Syntex notes that there are a number of Federal and local environmental, health and safety regulations with which Syntex must comply. It was obvious that a substantial cost of manufacturing cal pan at Syntex was due to these regulations, especially since the plant was built before the requirements were effective and, thus, were not provided for in the original design.

2/ Mar. 21, 1980, interview with Syntex officials.

3/ Ibid.

4/ Diamond Shamrock is not mentioned in Syntex' sec. 337 complaint.

intends to serve export as well as domestic markets. At present the plant is producing only animal-feed grade d-cal pan. If market conditions warrant such action, additional purification equipment can be added at a later date to produce U.S.P. pharmaceutical grade d-cal pan.

This plant was planned and built to replace Diamond Shamrock's Harrison, N.J. dl-cal pan plant which was considered by Diamond Shamrock to have become technologically obsolete. The dl-cal pan plant was closed in 1975.

Diamond Shamrock licensed technology known as the "Jenapharm" process named after the East German company. 1/ The technology is covered in U.S. Patents 4,111,987 and 4,115,443, dated September 9, 1978. 2/ The key feature of the Jenapharm process is a method of separating the optical isomers by using lithium carbonate. Since the l-isomer is physiologically inactive, it is racemized and recycled, thus giving much better utilization of the starting materials. In a dl-cal pan plant, half of the raw materials and cost of production are wasted producing l-cal pan, which is inactive.

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The plant appears to be well planned, though exceedingly complex, and many features, such as those for environmental and pollution control, were anticipated and incorporated into the original design. The plant also has a well-equipped analytical and quality control laboratory with excellent modern instrumentation. 3/

The basic chemistry of the synthesis of dl-pantolactone is the same as that used by Syntex, except that in the Jenapharm process the crude pantolactone is reacted with lithium carbonate. The resulting d-lithium pantolate can be resolved and separated from l-lithium pantolate by a carefully controlled crystallization procedure whereby the d-lithium pantolate is converted back to d-pantolactone while the l-lithium pantolate is racemized and recycled.

1/ See the previous discuss about the Jenapharm process on p. 4 of this report.
2/ See exhibit B.
3/ Exhibits C and D outline the chronological development of the plant and provide some statistical data about the plant and its process outline.

* * * * * * *

Diamond Shamrock uses some of the output from its d-cal pan plant in its adjacent animal-feed premix plant. The d-cal pan is mixed along with various other vitamins, choline chloride, and occasionally other medicinals such as antibiotics to produce premixes with various concentrations of medicinals. Premixing is a relatively simple operation in which the medicinal chemicals, including vitamins, are diluted in a high speed screw mixer with inert carriers such as rice hulls, corn cobs, etc. At the premix level, cal pan loses its product identity as a separate chemical. From this point forward the price of the premix includes not only the cost of d-cal pan, but the cost of other vitamins, and the additional costs of mixing, carrying, and packaging.

C. Synthesis of d-cal pan at the Daitom Plant, Mo. 1/

Around 1970 Daiichi Seiyaku Co., Japan, developed and patented a process to produce d-cal pan. 2/ Thompson-Hayward, a large importer of cal pan, became interested in building a plant using Daiichi technology. A joint venture was therefore formed between Thompson-Hayward and Daiichi, with the resulting company called Daitom.

Acquisition of the plant site was assisted by low-interest bonds issued by Kansas City. Kem Tech. Inc. was selected to handle overall construction of the project. The plant began operating in May 1978. The design capacity is 480 metric tons per year, and cost of construction has well exceeded * * *. In view of the greater biological activity and concentration of d-cal pan, the Daiichi patented process to produce d-cal pan has a theoretical cost-of-production advantage over a plant that produces dl-cal pan.

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The Daiichi patents are based upon the discovery that either d- or l-cal pan can be selectively crystallized from a solution rich in the same isomer by seeding the solution with pure crystals of the isomers. The pure d-cal pan is crystallized from a solution rich in d-isomer, and in another vessel, l-cal pan is crystallized from a solution rich in l-isomer. The physiologically active d-cal pan is then

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1/ The Daitom plant is not mentioned in Syntex' sec. 337 complaint.

2/ See exhibit B.

dried and packaged for sale. The l-cal pan is dried and then heated in the presence of a sodium methylate catalyst which converts the l-cal pan to a racemic mixture, dl-cal pan. This is then recycled back through the resolution process. Separation of the d and l-cal pan in the Daitom plant is said to be more of an art than a science, and the crystallization of d-cal pan, which takes * * * hours per batch, must be carefully controlled.

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Daiichi Seiyaku Co. does not presently make d-cal pan, but its subsidiary, Fuji Chemical Industries, does. 1/ Fuji resolves dl-pantolactone into d-pantolactone and l-pantolactone. 2/ The d-pantolactone is reacted with beta-alanine and calcium to produce d-cal pan, while l-pantolactone is converted to dl-cal pan.

1/ Conversation with Mr. Onashi on Apr. 24, 1980, at Daitom plant in Kansas City.

2/ Ibid.

III. The structure of the U.S. cal pan market

During the past decade, the market structure of the cal pan industry consisted of three to six producing firms. Such a market structure is defined in economic terms as an oligopoly, of which the basic nature is that a small number of firms supply most or all of the industry output and a varying mixture of monopoly and competition exists. A patented technology or complex production process often creates an oligopolistic market structure. Frequently, a firm or several firms hold a dominant market position, while limited price competition and attempts at price leadership by a dominant firm characterize such a market. Barriers to entry are another contributing condition for oligopoly. New entry must be relatively difficult. The above is an apt description of the cal pan industry market structure.

Currently, three firms, Syntex Agribusiness Inc., Diamond Shamrock Corp., and Thompson-Hayward Corp., supply the market with domestically produced cal pan. A high degree of concentration existed in the cal pan industry in the 1970's, when much of the time Syntex had a virtual monopoly of domestic supply and held a dominant market position. The same firm exercised a price leadership role with varying degrees of success during this period. The nature of cal pan as a uniform or fungible product created, to some extent, what is called in economic theory a "pure oligopoly." Competition in such a market structure is largely based on price rather than product differentiation. Attempts to "differentiate" the product hinged on service, dependability, quality, and proximity of supply. More recently, however, technology change in the production process has altered the market structure to one of more "differentiated oligopoly." The product has, in d-cal pan form, taken on what is in a real sense an element of differentiation, namely, lack of hygroscopicity. Consequently, competition between producers of d-cal pan and dl-cal pan consists of an added dimension of extra product quality (based on inherent product characteristic) as opposed to being made up of the price factor alone.

Barriers to new entry have indeed characterized the cal pan industry and include the technology of the production process (a closely held, patented chemistry), associated high capital investment requirements, the uncertainties of demand as a result of cyclical downturn (1975-76) and the growing import competition, shortages of key inputs, and the very high costs of meeting environmental pollution control requirements. As a result, the domestic market structure of the cal pan industry has remained one of oligopoly.

A. The producers of cal pan

From 1974 to the present, the structure of the cal pan market has changed significantly. The market profile of producers (and suppliers) has been altered by acquisition, attrition, permanent exit, exit and reentry, relocation of facilities, and by elimination of specific grades of cal pan from several firms' production line. Market factors contributing to the dynamic change in the domestic industry structure were the nature of the product cycle in this segment of the vitamin industry, accompanying changes in state-of-the-art technology, the heavy burden of costly environmental and health regulations, the business cycle, rising costs of inputs (especially energy), import competition, and full-line marketing necessities.

There were six firms engaged in the production of cal pan in the early 1970's. Those companies included Syntex Agribusiness Inc. (Springfield, Mo.), Diamond Shamrock Corp. (Harrison, N.J.), Dawes Labs (Chicago, Ill.), Peter Hand Corp. (Waukegan, Ill.), Chemlek Corp. (Aslip, Ill.), and Thompson-Hayward (Kansas City, Mo.). Syntex at that time manufactured both d-cal pan and dl-cal pan, and then converted a portion of the latter into production of cal pan complex. The remaining five companies produced only dl-cal pan and cal pan complex.

Market analyses by Diamond Shamrock and by Stanford Research Institute 1/ indicate that the industry structure shifted drastically during 1975-77. By 1975, Thompson-Hayward had acquired the Peter Hand Corp., and by the following year, only Syntex produced dl-cal pan. Syntex, in turn, discontinued production of d-cal pan in 1976.

The following tabulation shows the changing pattern of domestic suppliers producing both d- and dl-cal pan from 1970-80:

1970	1975	1976	1980
Diamond Shamrock	Diamond Shamrock	-	Diamond Shamrock
Hoffman-Taff 2/	Syntex Agr.	Syntex Agr.	Syntex Agr.
Dawes	Dawes	-	-
Chemlek	Chemlek	-	-
Peter Hand	-	-	-
Thompson-Hayward	Thompson-Hayward	-	Thompson-Hayward (Daitom)

1/ See exhibits E and F.

2/ Includes both captive and merchant sales.

Dawes International has ceased producing cal pan but is still a supplier, presently buying domestically, and also marketing imported cal pan. Chemlek is also no longer producing cal pan, and although the firm had purchased from * * *, it is reportedly a present customer of * * *.

Diamond Shamrock, which existed as a dl-cal pan producer in 1976, has re-entered the market as a producer of d-cal pan. Diamond Shamrock still buys dl-cal pan * * *. Thompson-Hayward bought out Peter Hand, and then ceased production of dl-cal pan in 1976. It later re-entered the market as a d-cal pan producer via a joint venture with the Japanese company, Daiichi, creating the Daitom Corp. in Kansas City, Mo. * * *

Industry estimates of the market shares by sale of the domestic suppliers of cal pan 10 years ago versus current shares by sale are presented in the tabulation below.

Market shares 1/ 10 years ago 2/	Current market shares 3/
Syntex - ***	Syntex - *** 4/
Diamond Shamrock - ***	Thompson-Hayward - *** 4/
Dawes - ***	Hoffman-LaRoche - *** 4/
Chemlek - ***	Diamond Shamrock - *** 4/
Peter Hand - ***	Direct Import-Brokers ***

1. Imports' share of the U.S. market for dl-cal pan.--Estimated market shares of imports of dl-cal pan are presented in table 1. U.S. production plus estimated imports of dl-cal pan are the basis for calculating the share of the U.S. market accounted for by imports. In turn, the total import share is disaggregated to show the market share of dl-cal pan imported from Japan and all other countries. The estimates of U.S. imports of dl-cal pan are based on the net import file of the U.S. Customs Service.

During 1977-79, Syntex Agribusiness was the only domestic producer of dl-cal pan. The data indicate that Syntex' market share fell from *** to *** as production declined steadily from a 1977 level of *** pounds to *** pounds in 1979. By contrast, imports of dl-cal pan increased *** from *** to *** pounds during that period, and the market share of imports climbed from *** to ***. Imports from Japan accounted for most of this increase in imports' market share, rising from *** pounds (1977) to *** pounds (1979), after dropping to *** pounds in 1978. Slightly more than *** the U.S. market in 1979 was supplied by dl-cal pan imported from Japan.

1/ Includes both captive and merchant sales.
2/ Estimate of Syntex Agribusiness.
3/ Estimate of Diamond Shamrock Corp.
4/ Includes imports for captive use or resale.

2. Imports' share of the U.S. market for d-cal pan.--There was no domestic production of d-cal pan in 1977 or 1978. Imports supplied the entire market. The imports of d-cal pan from Japan dominated the market, accounting for *** and *** in 1977 and 1978, respectively (table 1). In 1979, the Thompson-Hayward new plant began commercial operation and produced, *** pounds almost *** of the total U.S. market for d-cal pan. Japan's 1979 market share fell to *** of the U.S. import market. On the basis of the domestic production of d-cal pan during January-June 1980, the market share supplied by domestic production of d-cal pan will * * * in 1980. Concomitantly, the market share for imports probably will fall sharply to a range of *** to *** and Japan's market share may * * * .

As previously described, cal pan is used in pharmaceutical vitamins (and food products) for humans and in animal-feed. About 10 years ago the domestic consumption of cal pan was approximately 900 to 1,000 metric tons (96 percent d equivalent), of which 300 tons was targeted for human consumption, the balance being for animal consumption. Presently, cal pan consumption in the United States is estimated at approximately 1,450 metric tons, of which 350 metric tons is designated for human use, the balance being for animal usage. As can be seen from these figures, over the entire period, the human consumption market did not grow nearly as fast as the animal nutrition side of the market. Cal pan use as an animal feed additive increased roughly 64 percent in the past decade, compared with about a 17 percent increase in the pharmaceutical or human vitamin use of cal pan. More recently, however, according to industry sources, market growth in the pharmaceutical grade of cal pan has outpaced that of the animal-feed market segment.

3. Syntex Agribusiness, Inc.--Syntex was originally a Mexican company which pioneered in the research and development of steroids for hormonal applications. Once the research and development was completed, subsequent large-scale production began. The firm presently is a multinational company registered in Panama for tax purposes. The U.S. corporate headquarters is in Palo Alto, Calif., * * *. Syntex' entry to the cal pan market was accomplished by acquisition of the Hoffman-Taff company.

Hoffman-Taff was headquartered in the Springfield, Mo. area, and also had all of its production facilities located in that city. This company specialized in synthetic organic chemicals, and had been producing cal pan since the early to mid-1950's. During these early years (1950-65) Hoffman-Taff was the dominant firm in the market for cal pan, holding a market share as high as ***.

Table 11.--Dl- and d-calcium pantothenate: Domestic production, imports from Japan and all other countries, total U.S. market, and imports' market share, 1977-79

Type and year	Domestic production 2/	Imports 1/			Total U.S. market	Market share of imports		
		Total	From Japan	From all other countries		Total	From Japan	From all other countries
	1,000 pounds	1,000 pounds	1,000 pounds	1,000 pounds	1,000 pounds	Percent	Percent	Percent
Dl-cal pan:								
1977---	***	***	***	***	***	***	***	***
1978---	***	***	***	***	***	***	***	***
1979---	***	***	***	***	***	***	***	***
1980---	3/ ***	-	-	-	-	-	-	-
D-cal pan:								
1977---	4/	***	***	***	***	***	***	***
1978---	4/	***	***	***	***	***	***	***
1979---	5/ ***	***	***	***	***	***	***	***
1980---	6/ ***	-	-	-	-	-	-	-

1/ Imports of dl-cal pan were estimated by applying the percent share of dl-cal pan imports as calculated from the net import file of the U.S. Customs Service to the total U.S. imports of cal pan shown in official statistics of the U.S. Department of Commerce.

2/ Syntex was the only producer of dl-cal pan during this period.

3/ Syntex' 1980 production projected from actual production Jan.-July 31, 1980.

4/ No domestic firms produced d-cal pan in 1977 or 1978.

5/

6/ Domestic production projected from actual production, Jan. 1-June 30, 1980.

Source: Domestic production as reported by Syntex; import statistics estimated from the net import file of the U.S. Customs Service and official statistics of the U.S. Department of Commerce.

Syntex Agribusiness is composed of three divisions: the Vitamin and Nutrition Division in Springfield, Mo., the Animal Health Division in Des Moines, Iowa, and the International Division in Palo Alto, Calif. The International Division essentially markets the products of the other two divisions of Syntex Agribusiness. The Vitamin and Nutrition Division is composed of two production facilities, one of which is located in Springfield, Mo. (the former facilities of Hoffman-Taff), and also a plant located in the nearby area of Verona, Mo. The Springfield facility manufactures dl-cal pan and was also the facility where Syntex once produced d-cal pan. The Verona facility manufactures lactone and calcium chloride complex.

4. Diamond Shamrock Corp.--The Diamond Shamrock Corp., a large profitable conglomerate with extensive international operations, serves the cal pan market through its agricultural and health products division. 1/ The animal nutrition segment of the company's business increased significantly as a result of the purchases of Shell Chemical's animal health operations in mid-1979. The acquisition gave Diamond Shamrock a strengthened marketing structure and a broader product line. During 1979, the firm began to use the first commercial production from its new cal pan plant in Van Buren, Ark.

Diamond Shamrock has three major regions wherein it has approximately * * * salesmen. Those regions are the west coast, the midwest, and the Southeast or mid-Atlantic States. All of the administrative and selling operations, as well as distribution operations, are located in corporate headquarters in Cleveland.

Diamond Shamrock's predecessor in the cal pan market was Nopco Chemical, which first produced cal pan in 1939-1940 at an approximate cost of $1.50 per kilo. Nopco has generally been regarded as one of the pioneers in the manufacture and production of cal pan. Nopco produced dl-cal pan--calcium chloride continuously until 1974. 2/ In 1968, Nopco was acquired by Diamond-Alkaline, which

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1/ This division generated $17.8 million in operating profit in 1979, representing a 41 percent increase over that in 1978. Strong performance in agricultural and increased export activity were the principal factors.

2/ Nopco made d-cal pan until the late 1950's and then dropped out of the market owing to the fact that producing the item involved very high unit costs.

later became Diamond Shamrock. During that relevant time period some of the other competitors in the cal pan market were American Cyanimid, Merck, 1/ Chemlek, Dawes Laboratories, and Hoffman-Taff (Syntex' predecessor).

Diamond Shamrock has never seriously produced U.S.P. grade d-cal pan, but has concentrated on cal pan for feed use only. In 1970, Diamond Shamrock had a significant market share, and its best selling product was a calcium chloride complex. This product was similar to the pantoplex product that was and still is manufactured by Syntex.

During its dormancy period, Diamond Shamrock lost a tremendous amount of its merchant sales because its competitors could buy d-cal pan from the same sources that were supplying Diamond Shamrock. Diamond Shamrock then decided to reenter the production of cal pan in order to reacquire its former status. The company sought to find a technology which was superior to the traditional dl-cal pan manufacturing approach, and that would also gain a raw-material advantage. This had to be coupled with the plan for a large enough plant to gain the economies of scale in order to serve a world market -- in other words, to have export capacity.

Upon the acquisition of the Jenapharm process, there was a corporate recommitment by Diamond Shamrock to the feed industry, and a drive to attain the number one spot in animal nutrition. * * * The cost of the new plant, which is now situated at Van Buren, Ark., was projected to be $10 million. * * * Diamond Shamrock feels that the Japanese have more costs involved in the production of d-cal pan than Diamond Shamrock. Their reasoning is that the new plant embodies excellent technology, that the oil situation is better domestically than in Japan, and that there are more pollution costs and problems in Japan.

1/ Merck was a small-capacity dl-cal pan producer via its European plant. It does not appear as a producer in recent market surveys.

* * * The capacity of the new plant is expected to be about 60 metric tons per month, leaving a significant amount of d-cal pan for an export market. The Commission staff was told that the plant is devoted exclusively to the production of d-cal pan, and is a state-of-the-art d-cal pan production facility. Diamond Shamrock emphasized that the plant is environmentally superior and that the firm has taken into consideration all possible contingencies.

5. Thompson-Hayward.--This firm is a subsidiary of North American Phillips Corp., one of the largest manufacturing companies in the United States. Thompson-Hayward is part of Phillips' Chemical and Pharmaceutical Group. 1/ The firm reported increased earnings in 1979 from animal health products business. Higher sales of animal nutrition and health products stemmed from "increased animal feed consumption as well as imported sales of d-cal pan." 2/

Thompson-Hayward initially participated in the cal pan animal-feed market as a marketer of nutrients for animal feed. It became a producer via the 1970 acquisition of a small competitor's operations. That firm, the Peter Hand Co., was basically a small premixing operation which produced vitamin D and cal pan which were sold individually and also used in premixes. This company started up its operation in 1948, the same time period as did Hoffman-Taff. In 1970, Peter Hand was buying domestic beta alanine and producing some cal pan, while on the other hand, it also purchased cal pan when there were ingredient shortages. Peter Hand was in the premix business to the extent that about * * * of the cal pan it produced was for captive use, and when it stopped producing, purchases were used captively.

Thompson-Hayward serves the U.S.P. or pharmaceutical cal pan market as well as the animal nutrient market. It markets a full line of U.S.P. grade vitamins, and a full line of additives for the feed market and for use in its captive and merchant premix operations. The firm purchases vitamins A, D, E, and B-12, as well as thiamine, ascorbic acid, and riboflavin, and produces choline and cal pan. * * * Thompson-Hayward covers the entire U.S. market by using * * * regional salesmen, * * * to * * * of which concentrate on the animal-feed market, while * * * to * * * concentrate on the U.S.P. grade cal pan market.

1/ The summary statement of the Chemical/Pharmaceutical Products Group shows operating income of $12.3 million in 1979 compared to $19.0 million in 1978. (North American Phillips Inc., Annual Report 1979, p. 26).

2/ Ibid., p. 27.

As previously noted, after ceasing production of dl-cal pan, Thompson-Hayward sourced * * *. According to Thompson-Hayward there are marketing benefits and necessities in being a producer of cal pan. [1] * * *

On the basis of this rationale and a decision to serve not only the domestic, but also the export market, Thompson-Hayward proposed the joint venture with Daiichi whereby a plant would be built here in the United States. After long negotiations, a joint venture, Daitom Corp., was formed in 1975. * * * Bond issues from Kansas City, Kan., were raised in order to help build the plant. Kintech of Cincinnati, Ohio, designed the plant, which began operating in April or May of 1978. The optimum design capacity was projected to be around *** metric tons per month. The cost of the plant was projected to be approximately * * *

6. Foreign producers supplying the U.S. cal pan market.--Five known foreign producers of cal pan serve the U.S. cal pan market. They include Hoffman-LaRoche from facilities in Scotland; Daiichi Seiyaku via its producing subsidiary Fuji Chemical Co.; and Alps Pharmaceutical Co. Ltd., like Fuji, exporting from Japan; Polfa, a producer located in Warsaw, Poland; and Chimionport, a Romanian producer. The discussion which follows is limited to the largest producers, i.e., Hoffman-LaRoche, Daiichi Seiyaku, and Alps.

a. Hoffman-LaRoche.--This firm is a major competitor in both the U.S.P. vitamin and the animal feed additives markets in the United States. Its sales volume in the latter market makes it the dominant firm, with an estimated greater-than-one-third share of the premix market, and a strong position in the feed mill business by virtue of the fact that it produces a broad line of feed additives. * * * Diamond Shamrock estimated that Hoffman-LaRoche currently has about * * * of the overall cal pan market. According to Thompson-Hayward, Hoffman-LaRoche is a fairly recent competitor in the animal-feed segment of the market, appearing as a market force less than 2 years ago.

Hoffman-LaRoche has consolidated and expanded its capacity by transferring production from its plant in Granzack, Switzerland, to its Dalry, Scotland, facilities.

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[1] An example is being able to supply customers' entire needs for vitamin supplements and additives.

* * * On the basis of current industry estimates, Hoffman-LaRoche (Roche Products) now has a capacity of * * * metric tons, approaching that of Daiichi's Fuji Chemical plant with * * * metric tons. The Dalry plant produces pantothene alcohol for use by the cosmetic and food industries.

b. Daiichi Seiyaku.--This Japanese pharmaceutical company is reputedly the dominant firm in terms of supplying the world cal pan market. In terms of value, Daiichi enjoys an estimated *** share of the total market. In 1970, Daiichi Seiyaku Co. developed and patented a process to produce d-cal pan which involved recovering d-cal pan from a racemix mixture. The patents were issued in 1972 (exhibit B). Originally, Daiichi's plant was located in Tokyo. According to Daiichi executives, in 1973-74, pollution requirements within the Tokyo Prefecture prompted a Government request to Daiichi to reduce production in its Tokyo plant. 1/ Under pressure to meet stringent, costly pollution control standards, Daiichi ceased production of d-cal pan at its Tokyo facility in the early part of 1975. * * *

Fuji was a larger producer of d-cal pan than Daiichi during the early 1970's. Fuji, the original producer of d-cal pan in Japan, made the product by a slightly different process than did Daiichi. 2/ Daiichi acquired Fuji in March of 1972 by * * * the only entity that producers U.S.P. grade d-cal pan, and its facilities are specifically dedicated to d-cal pan alone.

* * * * * * *

Since Thompson-Hayward had expressed an interest to Daiichi in promoting imported d-cal pan, Daiichi opted to also use Thompson-Hayward to market d-cal pan, especially in the animal feed market. As previously stated, this purchaser-

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1/ Meeting with Daiichi Seiyaku executives at Daitom Co. plant, Kansas City, Mo., June 18, 1980.
2/ Fuji presently uses the Daiichi technology.

seller relationship matured to a decision for the joint venture arrangement, * * *

Daiichi spokesmen state that the d-cal pan is or is becoming the preferred product, and the Daiichi marketing effort is directed toward only offering d-cal pan. Their presentation literature explains why d-cal pan is better, 1/ and the company sales thrust is designed not to sell by price but by quality. The market trend toward d-cal pan, Daiichi insists, confirms the success of this effort with the result that d-cal pan is in a stronger market position. Because of this shift in demand, the price of d-cal pan is going up, while the relative price of dl-cal pan is going down. Daiichi emphasizes that more than 50 percent of the U.S. cal pan market demand is for d-cal pan.

The European Community cal pan market (including associate members) has grown, according to Daiichi, to a level of demand slightly above that of the United States 2/ Japan does not fare as well in the European market because Hoffman-LaRoche is the largest d-cal pan producer in that market. 3/ In contrast, the two Eastern bloc producers' combined capacity, 1,100 metric tons, is in dl-cal pan. Daiichi estimates Hoffman-LaRoche production at about * * * metric tons per year, only *** metric tons of which go to the United States.

Although Daiichi agrees that EC brokers buy cal pan from Japan, Daiichi insists that it does not sell to EC brokers. However, Daiichi concurred with industry opinion that Japanese cal pan exported to the EC market is at times repackaged and transshipped to the U.S. market.

c. Alps Pharmaceutical Co. Ltd.--This firm is one of Japan's leading manufacturers and exporters of synthetic pharmaceutical chemicals and raw materials. It is a closely held corporation with a single person owning 50 percent of the shares. The company's two plants are located in central Japan in the city of Furukawa-Cho. Alp's principal products include berberin chloride, rutin, acopalamine butydromide, cal pan, and phenylpropanolamine hydrochloride. 4/ Approximately 60 percent of its production is exported.

1/ See exhibit G.

2/ Daiichi sees world demand as three times the size of demand in the U.S. market, i.e., world demand is about equally divided between the United States, the EC, and the rest of the free world. Market growth is also strong in Brazil and Argentina.

3/ Daiichi believes that Hoffman-LaRoche may use a similar process to that of Fuji Chemicals.

4/ State Department telegram, Osaka Kobe 1296, Nov. 16, 1979. Fiscal year 1978 (ending in March 1979) shows Alps sales of 5 billion yen. A Japanese banking source estimated that fiscal 1979 sales would increase to 5.4 billion yen with after-tax profits of about 400 million yen, or between 6 and 7 percent (exhibit H).

Recently Alps has expanded its cal pan production capacity to *** metric tons of dl- and *** metric tons of d-cal pan. According to Daiichi, Alps is continuing its expansion program and has completed a new beta alanine plant. 1/ * * *

* * * * * * *

B. The pharmaceutical market

The pharmaceutical companies have an inherent preference for d-cal pan, as only a small amount is needed for use in a vitamin pill. Clearly, the pharmaceutical houses are a more profitable segment of demand. They are able to sell the product in which they use d-cal pan at a higher price because the level of purification is that much higher. Syntex feels that the Japanese targeted the pharmaceutical industry first in their export efforts. Syntex stressed to the Commission staff that they had been forced out of the d-cal pan market, which, as previously stated, is a highly profitable one, especially when applied to human consumption. Syntex has served the pharmaceutical market with imports since it ceased production of d-cal pan.

All major domestic producers compete in the vitamin market. In the case of Thompson-Hayward (Daitom) and Diamond Shamrock, domestic production of d-cal pan is supplemented by imported d-cal pan. Hoffman-LaRoche buys some domestic d-cal pan and also imports d-cal pan from its plant in Scotland. Imported d-cal pan competition in this market also derives from 15 to 20 importers and brokers, among which are several Japanese trading companies and Daiichi, the world's largest producer of d-cal pan.

1/ A basic raw-material input for the production of cal pan. See p. 4.

All the major U.S. pharmaceutical houses are d-cal pan purchasers, as well as many independent vitamin manufacturers. Cosmetic firms also purchase minor amounts of d-cal pan. Estimates of market shares are difficult to assess from the interviews and submitted information. However, it is obvious from Commission staff interviews with Syntex, Diamond Shamrock, and Daitom that Hoffman-LaRoche holds the most significant share of the pharmaceutical market. The remaining small share would be distributed about evenly among the remaining three firms referred to above.

With respect to the U.S. human cal pan market, Thompson-Hayward believes that in 1974, consumption was around *** to *** metric tons, whereas today it is around *** metric tons. Insofar as U.S.P. grade cal pan for human consumption is concerned, the 1979 market shares would break out as follows: * * * The large markets for U.S.P. grade cal pan are where the "pill makers" concentrate. Those areas are New York, New Jersey, and California, because they are geographical locations with easy access to imported material. The Midwest also has a small market in this area primarily because Miles Labs and E. I. Lilly are located in that region. This market is also quite transitory in that most contracts do not last for more than 3 months as far as any particular price is concerned, and most buying is on a spot basis.

C. The animal nutrition market

As previously stated, cal pan is extensively used in the animal nutrition field, specifically for poultry and swine feed. Additionally, cal pan also is used in pet foods. With regard to the poultry and swine feed, large consumers of cal pan are feed mills. Ralston-Purina is the largest entity in the feed mill business and is typical of the general line feed mill. This company produces and sells all feeds through its own distributors and outlets. Ralston-Purina has approximately 75 mills, which buy the general ingredients and make premix of micro-ingredients (in grams) which are added to the feeds. Ralston-Purina buys two forms of cal pan from Syntex: Pantoplex 160, which has 160 grams of d-cal pan per pound standardization, as well as Pantoplex 80, which has 80 grams of d-cal pan per pound. The reason for the two different potencies is that some mills can handle higher potencies (Pantoplex 160), whereas others can only handle the lower potencies (Pantoplex 80). As a general proposition, feed mills do not buy d- or dl-cal pan, as the potency used in the feed itself is less than that of the two compounds.

* * * However, they do have a premixing operation that is located in Waukegan, Ill. According to Thompson-Hayward officials, there has been a *** maximum growth rate per year in the feed industry since 1974. They estimate the demand in the d-cal pan animal feed grain market in 1974 was approximately * * * metric tons. 1/ The market presently is approximately *** more than the 1974 figures. The United States

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1/ This estimate is higher than the general industry consensus of a high of *** metric tons in 1974.

is the largest market for cal pan, as it is more conscious of feed nutrition and vitamin additives for its poultry and swine. Thompson-Hayward estimated that the U.S. market for cal pan is probably equal to the rest of the world. By way of contrast, the staff was told at Diamond Shamrock that the U.S. consumes approximately one-third of the total 4,000-metric-ton world market.

With respect to the animal-feed market shares, the major domestic suppliers are Syntex, Diamond Shamrock and Thompson-Hayward. Hoffman-LaRoche is one of the largest importers of d-cal pan for the animal-feed market. About *** of dl-cal pan is imported through brokers according to statements made by Thompson-Hayward's personnel.

D. The premix market

Of all the animal feed vitamin supplements sold, about 50 percent are sold through premixers, 1/ and about the same amount are sold through feed companies. 2/ The premix companies primarily use cal pan in poultry feed. A good example of this would be Perdue Co., a full-scale poultry operation, which buys a premix to add to its feed. The premix market is shared by the following companies, ranked in order of current estimated market share.

Hoffman-LaRoche -- ***
Diamond Shamrock -- ***
Thompson-Hayward -- ***
Pfizer, Dawes, Merck, local and regional premixers -- ***

The local and regional premixers are not corporate operations but are basicially entrepreneurial entities which buy everything in the animal-feed business. These premixers are very competitive, generally serve a local area, and are particularly "price oriented." As indicated above, more than *** of the premix business is held by Pfizer, Dawes, Merck and the regional premixers, although it could be safely said that of this ***, the majority share is held by the local and regional premixers.

It should be noted that many of the customers of premixers use the premix in the captive sense, as in the case of Perdue. About 21 of the broiler chicken companies account for 65 percent of the entire integrated boiler industry. The turkey industry is almost as integrated and concentrated as the chicken industry.

Both imported and domestic cal pan lose their identity at the premix level, and therefore comparisons of competitive market position must end at that

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1/ For representative list of noncaptive premixers see exhibit I.
2/ Ralston-Purina makes up about 10 percent of this 50 percent.

level. Whereas feed mills cannot use d-cal pan because it is far too potent and concentrated, the premixer can utilize this potent compound. Since the premix business is highly specialized, it is better equipped to prepare a premix which is then sold to a captive user of feed. A few premixers buy concentrated d-cal pan or dl-cal pan, and then dilute it to compete with Syntex' Pantoplex 160 product. Examples of these premixers would be Qualitech, Cadco, and Vitamin Producers of Ohama, which are all regional premixers with respect to their market impact. Hoffman-LaRoche is dominant in the market structure, because it is a basic producer of the majority of ingredients which actually are used in the premix.

IV. Condition of competition

A. Demand for cal pan

Demand for cal pan is a derived demand that stems from the demand for and production of poultry and swine. To a lesser extent, demand for cal pan is dependent on the use of this product in a pharmaceutical grade for human vitamin consumption. The world cal pan market was estimated at about 3,100 metric tons (96 percent d-cal pan equivalent) in 1974. By 1977, an industry market study shows demand had climbed to about 3,300 metric tons. 1/ Pages 29 and 30 present the staff's breakout, by regions and by countries. Currently, demand is believed to be at about 4,000 metric tons.

Domestic industry sources are in close agreement that the U.S. cal pan market is at a level of about 1,450 metric tons, d-equivalent. 2/ Based on the Commission's measure of domestic sales in 1973 and 1974--1,217 and 1,219 metric tons, respectively -- U.S. demand for cal pan has increased roughly by 230 metric tons or at an average annual rate of 2.6 to 3.1 percent. The growth of U.S. demand appears to have slowed and perhaps even stagnated during the past year or two. With U.S. consumption levels of poultry and pork already at high levels and given a relatively stable U.S. population, industry sources estimate cal pan demand for the feed market to grow at a rate of no more than 3 percent. In contrast, the pharmaceutical (U.S.P.) segment of the U.S. market is expected to increase at a rate of 5 to 10 percent per year, or at about the same average growth rate as that in other vitamin markets. The value of the U.S. market on the basis of current prices, is estimated at $200 million. 3/

Western Europe is the other significant free-world market for cal pan. This market increased from an estimated 938 metric tons in 1974 to a level estimated equal to that of the U.S. market. A market study by Diamond Shamrock indicates the rapid growth of poultry and hog consumption in Western Europe during this period. 4/ According to Daiichi marketing experts, the European market is "a little larger than the U.S. market" 5/ although the U.S.P. element of demand is very small.

The cal pan market potential in the remainder of the free-world (on the basis of poultry and hog production, accounts for approximately one-fourth of the world total) depends largely on the policy in developing countries toward promoting grain feeding of livestock and on the pace of economic development in those countries. An optimistic 5% growth rate in the market for cal pan in the developing countries was forecast in a recent market study of the industry. 6/ In contrast, industry sources expect developing countries demand to grow at no more than 3 percent per year.

1/ See exhibits E and F.

2/ See exhibit J. Executives of Daiichi (*** owner of Fuji Chemical Industries, the world's largest cal pan producer) confirmed domestic industry estimates of the current size of the U.S. market at a meeting with the Commission staff, June 19, 1980, Kansas City, Mo.

3/ See exhibit J.

4/ See exhibit E.

5/ Interview, June 19, 1980, Daitom Corp., Kansas City, Mo.

6/ See exhibit E.

B. The supply of cal pan

Production capacity to supply the free-world cal pan market was estimated at between * * * and * * * metric tons (96 percent d-equivalent) in 1974. 1/ The sources and amounts of current capacity, by regions, countries, and producing firms, are presented in table 2 on pages 29-30.

New investment and expansion of existing plants in the United States has increased capacity (actual, planned, and in progress) from 740 metric tons in 1975 to slightly more than 2,000 metric tons as new investments reach full production capability. 2/ European and United Kingdom combined capacity has more than doubled, from 1,000 metric tons to 2,400 metric tons. 3/ In Japan, the expansion of capacity was less, increasing from 1,400 to 1,800 metric tons. Total world cal pan capacity, existent and planned has doubled since 1975, climbing from roughly 3,000 to 6,000 metric tons. 4/

Companies exiting from the domestic industry during 1975-77 pushed the U.S. demand/capacity ratio to a deficit position. According to many industry participants, the U.S. capacity remains short of demand. The two new U.S. plants should, when in full operation, provide an export surplus of roughly *** to *** of total capacity.

During the last half of the decade, supply in the overall world market was at various times only in the most precarious balance with demand. The level of world demand, estimated at about 4,000 metric tons in 1979, has not shown the expected growth rate; thus, given significant new capacity, there now exists a demand/capacity gap that could widen to an estimated *** to *** as current new capacity becomes fully operative. Given world economic conditions, it is not expected that this demand/capacity gap will narrow significantly in the next few years. 5/

In 1975, roughly one-fourth of the world capacity was in small-batch process plants producing 45 percent biologically active dl-cal pan. The industry study by Diamond Shamrock correctly predicted that such small-scale capacity would disappear by 1980. About 250 metric tons of 1975 capacity no longer exists in the U.S. 6/;

1/ See exhibit E.
2/ * * *
3/ European capacity includes production in Romania and Poland. Only part of this capacity supplies free-world markets.
4/ Excluding U.S.S.R. capacity.
5/ See exhibit E.
6/ Diamond Shamrock (*** metric tons), Chemlek (*** metric tons), and Thompson-Hayward (*** metric tons).

and an additional *** metric tons of pharmaceutical grade cal pan capacity was removed. 1/ In Japan, *** metric tons of d-cal pan capacity was taken out of production in 1976. 2/ An additional 220 metric tons of Japanese capacity listed in 1975 3/ does not appear in the 1980 summary. A small Canadian plant closed, cutting world capacity by 50 metric tons. Merck closed its European plant (50 metric tons), and the Roche facility in Switzerland (100 metric tons) is no longer listed in world capacity estimates.

1/ Dawes ceased operating in 1976.
2/ Daiichi's Tokyo plant closed in 1976.
3/ Iwashiro Pharmaceutical--description unknown.

Table 2.--Producers of calcium pantothenate, 1980

Continent and country	Capacity	Type
	Metric tons, 96 percent d-equivalent	
North America:		
United States:		
Syntex Agribusiness Springfield, Mo. & Verona, Mo.	800	dl-cal pan complex
Daitom Inc. Kansas City, Mo.	500 1/	d-cal pan
Diamond Shamrock Van Buren, Arkansas	720 1/	d-cal pan
Subtotal	2,020	
Canada:		
Delmar	2/	dl-cal pan
Mexico:		
Niasa, Mexico City	45	dl-cal pan
Total, North America	2,065	
Europe:		
United Kingdom:		
Roche Products Dalry, Scotland	1,400	d-cal pan
Poland:		
Polfa, Warsaw	400 3/	dl-cal pan
Romania:		
Chimienport, Bucharest	600 3/	dl-cal pan
Total, Europe	2,400	dl-cal pan

See footnotes at end of table.

Table 2.--Producers of calcium pantothenate, 1980--Continued

Continent and country	Capacity	Type
	Metric tons, 96 percent d-equivalent	
Asia:		
Japan:		
Alps Pharmaceutical, Takayama	435	100 d-cal pan 700 dl-cal pan
Daiichi Seiyaku, Toyko	4/	-----
Fuji Chemical Industries, Takaoka	1,385	d-cal pan
Subtotal	1,820	-----
Korea:		
Sampoong, Seoul	15	-----
Total, Asia	1,835	-----
Total, world	6,300	-----

1/ Announced expected capacity, currently only partially in operation.
2/ Exited from the industry.
3/ Poland and Romania each supply about 150 metric tons annually to the free world.
4/ Closed.

Source: U.S. Commerce Department and U.S. Tariff Commission statistics.

C. Imports of cal pan

Table 3 presents the quantity and value of imports of cal pan, by source countries. Data on imports of d- and dl-cal pan are not recorded separately in official statistics of the U.S. Department of Commerce. Such imports are included in data for all imports of cal pan under TSUSA item 437.8225. Thus, it is not possible to analyze the import patterns of d-cal pan and dl-cal pan accurately from total import statistics, especially imports sourced from Japan. Imports from some of the other countries can be identified as largely d-cal pan, e.g., the United Kingdom, or as largely dl-cal pan, e.g., Poland and Romania, on the basis of the fact that production in those countries is known to be only d-cal pan or dl-cal pan, respectively (table 2).

Total U.S. imports of cal pan more than tripled during 1974-79, increasing from about 687,000 pounds in 1974 to 2.5 million pounds in 1979 (fig. 1, p. 33). Japan is the dominant source country, accounting for roughly three-fourths to four-fifths of total imports in every year except 1975 (fig. 2, p. 34). In that year, following the U.S. Tariff Commission dumping finding, Japan's share fell to 31 percent of the total quantity of cal pan imports, and Poland accounted for 61 percent. In terms of quantity, cal pan imports from Japan have grown from about 0.5 million pounds in 1974 to almost 2 million pounds in 1979, and from $1.6 million to $7.6 million by value. The United Kingdom has recently emerged as the second most important source country. Its exports of cal pan to the U.S. market increased from less than 50,000 pounds (1978) to more than 240,000 pounds in 1979, or from a share of 2 to 10 percent. This reflects the increasing strength of Hoffman-LaRoche in the U.S. cal pan market.

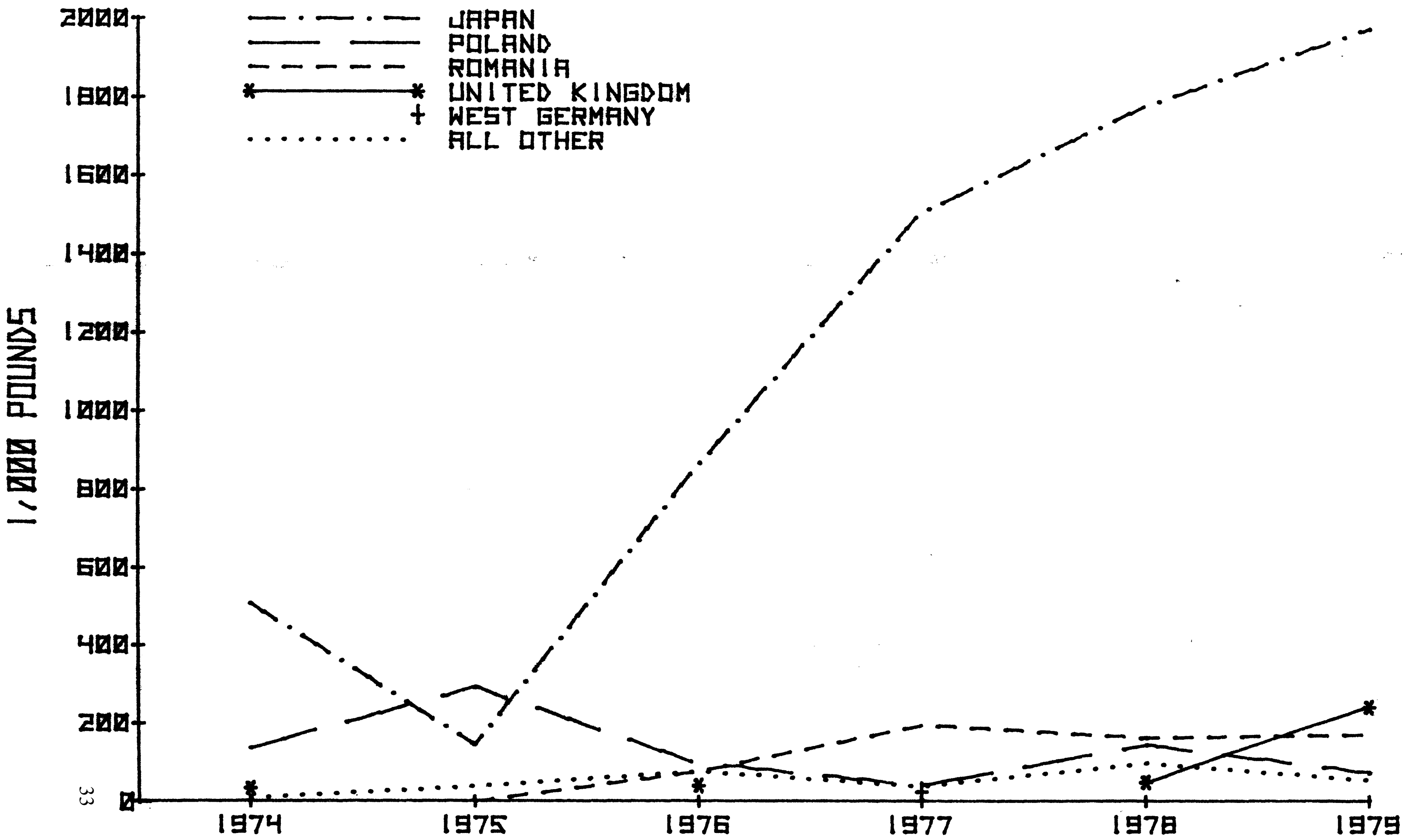
Using as a base the total U.S. imports of cal pan as compiled from the net import files of the U.S. Customs Service, the Commission staff disaggregated these imports into estimated U.S. imports of d-cal pan and dl-cal pan. Except for 1976, the total annual imports recorded in the net import file amounted to about *** to *** of the annual total quantity of imports shown in official statistics. Thus, the estimated shares of d-cal pan and dl-cal pan as disaggregated from the net import file should approximate their respective shares of total cal pan imports on the basis of official statistics.

Table 3.--Calcium pantothenate: U.S. imports, quantity and value, percent of total quantity, and percent of total value, by countries of origin, 1974-79

Year and source	Quantity	Value (c.i.f.)	Share of total quantity	Share of total value
	Pounds	1,000 dollars	Percent	Percent
1974				
United Kingdom	33,069	92	5	5
Poland	136,685	216	20	11
Japan	508,296	1,638	74	82
All other	8,763	39	1	2
Total	686,813	1,985	100	100
1975				
Poland	292,394	425	61	42
Japan	145,286	521	31	51
All other	38,581	78	8	7
Total	476,261	1.023	100	100
1976				
United Kingdom	39,682	97	3	3
Poland	96,562	145	8	4
Romania	77,161	97	7	3
Japan	860,724	2,886	75	86
All other	77,492	137	7	4
Total	1,151,621	3,361	100	100
1977				
West Germany	24,251	69	1	1
Poland	41,005	75	2	1
Romania	195,327	377	11	6
Japan	1,505,595	5,178	83	88
All other	38,833	212	3	4
Total	1,805,011	5,910	100	100
1978				
United Kingdom	48,117	251	2	3
Poland	144,268	230	6	3
Romania	161,622	311	7	4
Japan	1,779,144	7,330	80	86
All other	96,655	372	5	4
Total	2,229,806	8,494	100	100
1979				
United Kingdom	241,289	1,277	10	13
Poland	72,751	146	3	2
Romania	170,857	327	7	3
Japan	1,976,924	7,578	79	79
All other	54,588	285	1	3
Total	2,516,409	9,613	100	100

Source: Compiled from official statistics of the U.S. Department of Commerce.

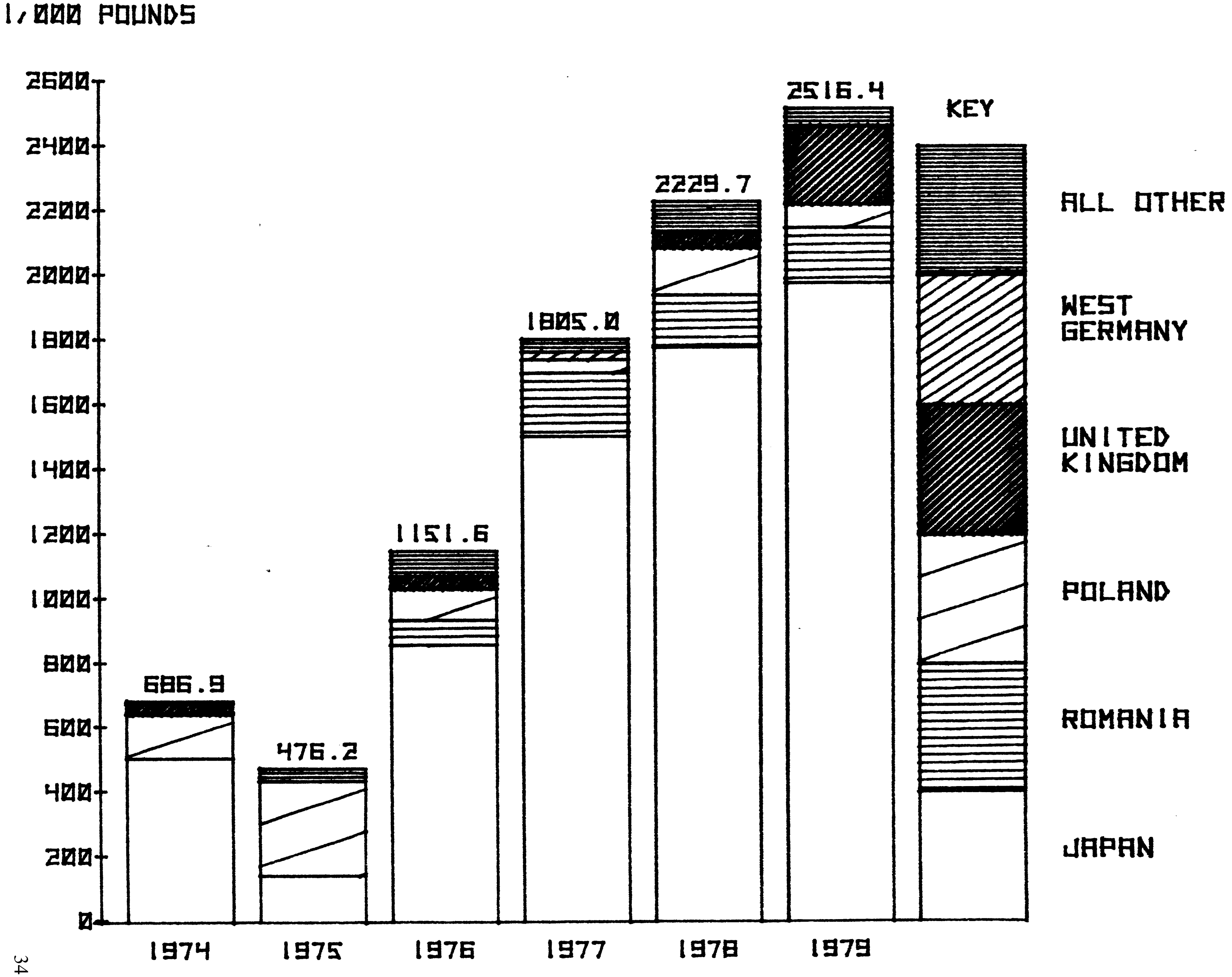
Figure 1.--Calcium pantothenate: U.S. imports for consumption, by principal sources, 1974-79.



Source: Based on data in table 3.

Note: There were no observations for imports from the United Kingdom during 1975 and 1976. The only observation for West Germany was during 1977.

Figure 2.--Calcium pantothenate: U.S. imports for consumption, by principal sources, 1974-79.



Source: Based on data in table 3.

These data are shown in table 4, p. 36 and indicate that the d-cal pan share of total cal pan imports moved upward irregularly from about *** in 1974 to about *** in 1978. 1/ In 1979, however, the d-cal pan share fell to about *** of total U.S. imports of cal pan. This probably reflects the increase in domestic supply of d-cal pan from the new production of the Daitom and Diamond Shamrock plants and the accompanying decline in those firms' imports of d-cal pan to supplement their supply requirements. The absolute decline in U.S. imports of d-cal pan from 1978 to 1979, however, was a result of a *** drop in imports from Japan, partially offset by a sharp rise in d-cal pan imports from the United Kingdom as Hoffman-LaRoche strengthened its market position. * * *

During 1974-79, U.S. imports of dl-cal pan have increased each year, from a level of *** kilos in 1974, valued at *** to *** kilos in 1979, with a value of *** Except for the previously noted decline in 1979, and a sharp fall in 1975, U.S. imports of d-cal pan climbed from *** kilos in 1974, valued at ***, to *** kilos in 1978, with a value of ***

D. The difficult competitive position of the domestic industry

1. * * * * * * *

1/ The shares of d-cal pan and dl-cal pan for 1975 and 1976 cannot be calculated from net import file data owing to the absence of figures on quantity and value of dl-cal pan imports in those years.

Table 4.--D- and dl-calcium pantothenate: U.S. imports for consumption from Japan and all other countries, by quantities, and by values, 1974-79

Year and source	D-calcium pantothenate			Dl-calcium pantothenate			Total calcium pantothenate			d- share of total quantity	dl- share of total quantity
	Quantity	Value	Share of total quantity	Quantity	Value	Share of total quantity	Quantity	Value	Share of total quantity		
	1,000 kilograms	1,000 dollars	Percent	1,000 kilograms	1,000 dollars	Percent	1,000 kilograms	1,000 dollars	Percent	Percent	Percent
1974											
Japan------	***	***	***	***	***	***	***	***	***	***	***
All other--	***	***	***	***	***	***	***	***	***	***	***
Total--	***	***	***	***	***	***	***	***	***	***	***
1975											
Japan------	***	***	***	1/	1/	1/	***	***	***	***	1/
All other--	***	***	***	***	***	***	***	***	***	***	***
Total--											
1976											
Japan------	***	***	***	1/	1/	1/	***	***	***	***	1/
All other--	***	***	***	***	***	***	***	***	***	***	***
Total--	***	***	***	***	***	***	***	***	***	***	***
1977											
Japan------	***	***	***	***	***	***	***	***	***	***	***
All other--	***	***	***	***	***	***	***	***	***	***	***
Total--	***	***	***	***	***	***	***	***	***	***	***
1978											
Japan------	***	***	***	***	***	***	***	***	***	***	***
All other--	***	***	***	***	***	***	***	***	***	***	***
Total--	***	***	***	***	***	***	***	***	***	***	***
1979											
Japan------	***	***	***	***	***	***	***	***	***	***	***
All other--	***	***	***	***	***	***	***	***	***	***	***
Total--	***	***	***	***	***	***	***	***	***	***	***

1/ There were no reported imports of dl-calcium pantothenate from Japan during 1975 and 1976.

Source: Compiled from statistics of the U.S. Customs Service.

* * * * * * *

2. The role of captive premix demand.--The cal pan market is characterized to a significant extent by domestic and importer operations which are integrated to include captive premix business. This pattern enables a multivitamin producer or importer to market a full product line. Consumers in the animal feed market and in the pharmaceutical or human vitamin market often tend to prefer dealing with a full-line supplier. Firms of significant market importance in the captive premix market are Diamond Shamrock and Hoffman-LaRoche. Syntex is not integrated into the captive premix market because of its limited product line.

Syntex used to have several premix plants throughout the country. There were two in California, located in Ontario and Turlock; the former was sold in 1975 and the latter in 1977, * * * There were also two other premix plants -- one located in Chattanoga, Tennessee, which was sold in 1978, and in West Alexandria, Ohio, which was sold in 1979. * * *

Before it went out of business, Diamond Shamrock had a captive premix use for cal pan that amounted to about *** to *** of its production. The remaining production output was a merchant product which was sold in arms-length transactions. According to Diamond Shamrock, the merchant product market markedly prefers to deal with a company which has a full line of additives. Therefore, after it ceased manufacturing cal pan, Diamond Shamrock was extremely concerned about the breadth of its product line, by which its prestige was measured in the eyes of purchasers.

A full line of additives is desirable for a company which manufactures animal nutrition products. It is apparently extremely important for a customer to believe that its additive supplier has three characteristics -- namely, dependability, reliability, and reliability of supply. Diamond Shamrock emphasizes that it is important to have cal pan in an animal nutrition line of the company. The Commission staff also was informed that one cannot remain viable in this business on the basis of one, or even just a few products, but must maintain a complete line of additive products.

* * * * * * *

The major business of Diamond Shamrock in the Animal Nutrition area is currently the premix business. * * * Diamond Shamrock now has three major premix operations, located in Van Buren, Ark., Louisville, Ky., and Fresno, Calif. However, the Commission staff was told that the west coast market is an entirely separate and distinct market. The firm's executives estimated that the west coast makes up about *** to *** of the total premix market because there is no grain produced in the Western States. Moreover, that area does not generate any significant volume in the rearing of poultry and swine, although it constitutes a large share of the egg market.

* * * Diamond Shamrock believes that Hoffman-LaRoche has about *** of the market and controls the pet food, broiler, and turkey market. Diamond Shamrock, on the other hand, plays a significant role in the layer market. With respect to the swine market, entities known as blenders purchase concentrate for additives to swine feed. Thus, in the swine market these are concentrates, compared with the premix markets, which are primarily devoted to poultry. In the swine market, the operator purchases a large quantity of concentrate which is blended with corn and soy meal in order to make the feed. A typical ratio would be from 100-400 lbs of concentrate to every ton of feed. On the other hand, in the premix area, the additives amount to approximately 2-5 lbs of vitamins per ton of feed.

3. * * * * * * *

4. <u>Competitive pressures from imports and costly EPA requirements</u>.--Syntex gave up domestic production of d-cal pan in part because of low-priced Japanese imports. Strong import price competition was also a factor in bringing about a situation where Syntex was left as the sole domestic producer of dl-cal pan. Diamond Shamrock, one of the earlier domestic producers of cal pan, had a dl-cal pan plant located in Harrison, N.J., which had an annual production capacity of about 350 metric tons. However, faced with old facilities and costly production control requirements in 1972-1973, there was some contemplation of locating a new plant at Texas for the production of dl-cal pan, but the proposal could not justify cost. At this time there were significant imports of Japanese cal pan, and the Japanese were further penetrating the market through sales of cal pan to Thompson-Hayward. Competition was intense, and at that time the domestic manufacturing cost of dl-cal pan was approximately $3.50 per kilo, while imported at $3.20 or $3.25 per kilo. The competition was so keen and one-sided as to prohibit any considerations of building a new plant.

In addition, regarding price competition, EPA requirements placed a heavy burden on Diamond Shamrock. In 1974-1975, Diamond Shamrock, reluctant to face the added burden of high pollution costs, decided not to build the new plant in Texas. Thus, in late 1974 to early 1975 Diamond Shamrock made the decision to leave the business of producing dl-cal pan. It should be noted that the equipment in that factory was dedicated to the production of dl-cal pan alone.

V. Cost of production of cal pan

Syntex, the sole domestic producer of dl-cal pan, provided cost of production data for 1973-80. After 1973, however, the data supplied by Syntex are hypothetical costs of production rather than actual costs. 1/ Their constructed costs are based upon what they expected their costs to be if using the * * * process to make beta-alanine, while in fact, they have been using * * * to make dl-cal pan.

In 1973, Syntex was making beta-alanine by a process which used beta-alanine propiolactone. As noted earlier, beta-propiolactone was found to be a potent cancer-causing agent, and in 1974, Celanese stopped producing the material and supplying it to Syntex. * * *

Syntex supplied a history of the prices it paid for beta-alanine. 2/ Syntex also supplied standard cost sheets. 3/ The Commission staff was, therefore, able to estimate the actual U.S. cost of production of dl-cal pan, except for 1975 and 1976. The results are shown and in table 5, p. 42.

1/ Reference is made to Syntex' sec. 337 complaint, its attachments, and documents furnished by Syntex.
2/ See exhibit K.
3/ See exhibits L and N.

A. Factors affecting Syntex's costs

Some of the factors affecting Syntex's costs were discussed in the preceding section concerning the difficult competitive position of the domestic industry. Other factors are discussed hereinafter.

1. Food & Drug Administration health regulations.--Syntex changed its cal pan production process following a Government ban on beta-propiolactone, an output chemical found to be a potent carcinogen. * * *

2. Compliance with Environmental Protection Agency and Occupational Safety & Health Adminstration regulations.--Another significant factor which was apparent to the Commission staff during its visit to the Syntex Springfield plant was that there were a multitude of Federal Government environmental, health, and safety regulations which Syntex has to comply with. The primary agencies involved in such regulations would be Environmental Protection Agency, Food & Drug Administration and Occupational Safety & Health Administration. The Commission staff was informed that in recent years compliance with these regulations constituted a substantial cost factor in Syntex' dl-cal pan production. The environmental costs in Japan are not known by Syntex, but according to some of their people, the cost may be less, as plants in Japan are generally located away from populated areas.

3. Import price competition.--The reaction process used by Syntex yields a racemic mixture of dl-cal pan. At one time Syntex separated some of the material and isolated the d-cal pan which is the only isomer with physiological activity. Syntex ceased production of d-cal pan in 1976 because it was not price competitive with imports from Japan. * * *

Up until 1979, Syntex produced a pharmaceutical grade of dl-cal pan which required additional purification steps not required for the animal feed grade material. Since d-cal pan is the preferred material for use in human vitamin formulations, Syntex discontinued production of the medicinal grade dl-calcium pantothenate, * * *

During its visit to Syntex, the Commission staff was given the impression that Japanese resolution processes are more economical than that of Syntex. This conclusion was confirmed by the staff visits to the Thompson-Hayward Co. in Kansas City and to Diamond Shamrock in Cleveland, as well as at the staff meeting with Daiichi officials from Japan.

Table 5.--Estimated U.S. cost of production of dl-calcium pantothenate, beta-alanine and pantolactone, fiscal years, 1973-80 1/

Fiscal year	Cost of--			
	Beta-alanine	Pantolactone	Other	Dl-calcium pantothenate
1973	1/ ***	***	***	***
1974	3/ ***	***	***	***
1975	4/	***	***	4/
1976	4/	***	***	4/
1977	5/ ***	***	***	***
1978	5/ ***	***	***	***
1979	5/ ***	***	***	***
1980	5/ ***	***	***	***

1/ Fiscal year is Aug. 1-July 31.

2/ Produced by Syntex.

3/ From inventory.

4/ Not available, but could have been inordinately high because of cost associated with the attempt to change the beta-alanine synthesis process.

5/ Imported from Japan.

4. FDA action in the human vitamin market.--According to Syntex, the pharmaceutical market for cal pan was adversely affected by an FDA ruling in the mid-1970's. The FDA had listed cal pan as an alternate ingredient for inclusion in vitamins. One other alternate was biotin, which had to be included according to the FDA regulation. Since it was priced at $10 a gram, prohibitive expense prompted the vitamin people to decide against the use of cal pan. Although the FDA was not successful in promulgating this list, Syntex contends that most of the vitamin manufacturers did not use d-cal pan, and have not since returned to its use.

B. Cost of production for Daitom

* * * * * * *

Officials at Daitom and Thompson-Hayward nonetheless stressed that they had a cost-efficient operation. The cost advantage that was stressed is the utilization and racemization of the l-molecule to connect it to the d-molecule--a unique process according to Thompson-Hayward. In order to achieve the maximum or optimum design capacity of *** tons a month, the plant must produce * * * lbs. of dl-cal pan, which would yield * * * lbs. of d-cal pan. A producer who could not get anything out of the l-molecule would only get * * * lbs. of d-cal pan, or half of * * * lbs. of dl-cal pan. * * *

* * * * * * *

The Commission staff was informed by the technical people that maximum utilization of raw materials occurs when d-cal pan is manufactured by Daiichi's process. Apparently, with the more esoteric technology, the trend is toward the manufacture of the purer grade of d-cal pan. * * *

C. Cost of production for Diamond Shamrock

As noted earlier in this report, there has not been enough experience in the operations of Diamond Shamrock's plant to arrive at any meaningful cost of production figures.

D. Cost of imported cal pan

1. The level and competitive impact of alleged low-priced imports.--Data on the range and weighted average, prices paid by importers, f.o.b. port of lading, are presented in table 6 for d-cal pan and in table 7, p. 46 for dl-cal pan. The weighted average landed, duty-paid cost has been estimated from official statistics of the U.S. Department of Commerce. In order to focus on the level and competitive impact of alleged extremely low (below-cost) pricing of imported cal pan, the table also includes the weighted average f.o.b. value and c.i.f., duty-paid value of the cal pan imported by the importers in the lowest one-third of the import price range. These unit values were calculated from line item entries by specified importers as listed in the net import file of the U.S. Customs Service.

2. The average price (unit value) of imported d-cal pan.--The weighted average landed price (duty-paid, port of entry) for d-cal pan sourced from Japan increased *** during 1974-79, or from *** per kilo to *** per kilo (table 6). The recession impact on price, reflecting the decline in demand, is apparent in 1975 and 1976 in importers' weighted average landed cost of *** and *** per kilo, respectively. In 1974, the weighted average landed cost of the firms in the lowest one-third of the range was *** per kilogram, or *** below the weighted average cost of all importing firms. The difference in average landed cost for all firms (***) and for those in the lowest one-third of the range (***) had narrowed to about *** in 1979.

Imported d-cal pan from sources other than Japan was sold at an average landed cost consistently below the Japanese product except in 1977 and 1978 (table 6). The competitive cost advantage of d-cal pan imported from non-Japanese sources ranged from a high of *** in 1976 to a low of *** in 1979. * * * The cost advantage was as much as *** to *** during the recession years 1975-76, averaging *** in the other years except for 1978, when non-Japanese sourced imports reflect an average landed cost only *** below d-cal pan imported from Japan. In 1979, average landed duty-paid importers' cost of non-Japanese sourced d-cal pan was *** per kilogram compared with *** per kilogram for the product imported from Japan.

It should be noted that d-cal pan is produced in only two countries, Japan and Scotland. Therefore, it is entirely possible that imports sourced from countries other than those, such as Denmark, West Germany, Israel, etc., are transshipments wich may have originated from Japan or from Scotland. Imports of d-cal pan from countries other than Japan totaled about *** kilograms or about *** of total imports (*** kilograms) and about the same share by value. Almost *** of these non-Japanese sourced U.S. imports came from the Hoffman-LaRoche plant in Scotland.

Table 6.--D-calcium pantothenate: Range and weighted average unit values of imports from Japan and all other countries, 1974-79

(Per kilo)

Source and unit value	1974	1975	1976	1977	1978	1979
Japan:						
Range of firms' unit value (f.o.b.):						
High	***	***	***	***	***	***
Low	***	***	***	***	***	***
Weighted average unit value of all firms:						
F.o.b	***	***	***	***	***	***
C.i.f + duty 1/	***	***	***	***	***	***
Weighted average unit value of firms in the lowest 1/3 of range: 2/						
F.o.b	***	***	***	***	***	***
C.i.f + duty 1/	***	***	***	***	***	***
All other:						
Range of firms' unit values:						
High	***	***	***	***	***	***
Low	***	***	***	***	***	***
Weighted average unit value of all firms:						
F.o.b	***	***	***	***	***	***
C.i.f. + duty 1/	***	***	***	***	***	***
Weighted average unit value of firms in the lowest 1/3 of range: 3/						
F.o.b	***	***	***	***	***	***
C.i.f + duty 1/	***	***	***	***	***	***

1/ C.i.f. values were estimated using official statistics of the U.S. Department of Commerce. Column 1 duty rates on calcium pantothenate (TSUSA item 437.8225) are 4 percent ad valorem for countries with MFN status (Japan, United Kingdom, Netherlands, Republic of Korea, Federal Republic of Germany, Switzerland, Spain, Canada, Denmark, Poland, and Italy). The column 1 duty rate for Hungary is 25 percent ad valorem. Since 1977, imports from Israel have not been subject to duty because of the country's GSP status. Imports from Romania were subject to a 25-percent ad valorem duty in 1974 and 1975. During 1976, imports from Romania entered at 3 duty rates: (1) 25 percent, (2) 4 percent MFN status, and (3) free of duty because of GSP status. The majority of Romanian imports during 1977 and 1978 entered under GSP status, while the remainder were assessed 4 percent. All Romanian imports entered under GSP status during 1979.

2/ Based on exhibit N.

3/ Based on exhibit N.

Source: Compiled from statistics of the U.S. Customs Service.

The data in table 7 indicate a steady rise in the price of dl-cal pan. The weighted average, landed, duty-paid cost to the importers of dl-cal pan sourced from Japan increased *** during 1974-79, or from *** per kilogram to *** per kilogram. In 1979, the landed cost of the firms in the lowest one-third of the range of unit values averaged *** per kilogram, or *** lower than the average for all firms importing from Japan.

Imported dl-cal pan from countries other than Japan has entered the U.S. market in 1978 and 1979 at landed costs lower than dl-cal pan sourced from Japan. The average landed importers' cost in 1978 was *** per kilo from Japan and *** per kilo from other source countries; the competitive cost per kilo in 1979 was *** from Japan and *** from other sources. In earlier years the dl-cal pan imported from Japan was brought in at *** to *** below competing imports from other source countries. Comparing dl-cal pan imports by firms in the lowest one-third of the price range, the average landed (duty-paid) cost of the product imported from Japan was *** above that of product sourced from other countries in 1978 and *** higher in 1979. Import price pressure in the dl-cal pan market has apparently received considerable impetus from shipments originating from countries other than Japan.

The range of export values, f.o.b. port of lading of Japanese exports of dl-cal pan reflects price differences to importers of as much as * * * per kilogram (1977), * * * per kilogram (1978) and * * * per kilogram (1979). Price differences reflected in the range of export values of imports from countries other than Japan were * * * per kilogram (1977), * * * per kilogram (1978) and * * * per kilogram (1979).

3. <u>The landed cost (duty-paid) of dl-cal pan to specific importing firms</u>.-- Tables 8 and 9 present data calculated from the net import file on the landed cost, by named importer, of those firms in the lowest one-third of the range of f.o.b. export values of U.S. imports of dl-cal pan. These data also provide the ratio of a specific firm's imports, by quantity, to the total quantity of imports recorded in the net import file.

4. <u>Landed cost of dl-cal pan imports sourced from Japan</u>.-- * * * is the only firm appearing as a low-priced importer of Japanese dl-cal pan throughout period 1974-79 (table 8). Data is meager in the year 1974-76, but in 1977 the low-priced imports of Japanese cal pan came from * * * Since 1977, * * * share of total imports of the product sourced from Japan has declined to about *** in 1978 and *** in 1979. The number of importers of dl-cal pan has increased progressively. * * * Firms in the lowest one-third of the range

Table 7.--Dl-calcium pantothenate: Range and weighted average unit values of imports from Japan and all other countries, 1974-79

(Per kilo)

Source and unit value	1974	1975	1976	1977	1978	1979
Japan:						
Range of firms' unit value (f.o.b.):						
High	***	***	***	***	***	***
Low	***	***	***	***	***	***
Weighted average unit value of all firms:						
F.o.b	***	***	***	***	***	***
C.i.f + duty 1/	***	***	***	***	***	***
Weighted average unit value of firms in the lowest 1/3 of range: 2/						
F.o.b	***	***	***	***	***	***
C.i.f + duty 1/	***	***	***	***	***	***
All other:						
Range of firms' unit values:						
High	***	***	***	***	***	***
Low	***	***	***	***	***	***
Weighted average unit value of all firms:						
F.o.b	***	***	***	***	***	***
C.i.f. + duty 1/	***	***	***	***	***	***
Weighted average unit value of firms in the lowest 1/3 of range: 3/						
F.o.b	***	***	***	***	***	***
C.i.f + duty 1/	***	***	***	***	***	***

1/ C.i.f. values were estimated using official statistics of the U.S. Department of Commerce. Column one duty rates on calcium pantothenate (TSUSA item 437.8225) are 4 percent ad valorem for countries with MFN status (Japan, United Kingdom, Netherlands, Republic of Korea, Republic of Germany, Switzerland, Spain, Canada, Denmark, Poland, and Italy are sources of pantothenate with MFN status). The column one duty rate for Hungary is 25 percent ad valorem. Since 1977, imports from Israel have not been subject to duty because of GSP status. Imports from Romania were subject to a 25-percent ad valorem duty in 1974 and 1975. During 1976, imports from Romania entered at 3 duty rates: (1) 25 percent, (2) 4 percent MFN status, and (3) free of duty because of GSP status. The majority of Romanian imports during 1977 and 1978 entered under GSP status, while the remainder were assessed 4 percent. All Romanian imports entered under GSP status during 1979.

2/ Based on exhibit N. In 1974, only Mitsui appears in the net import file.

3/ Based on exhibit N.

Source: Compiled from statistics of the U.S. Customs Service.

of f.o.b. export values of dl-cal pan imported into the U.S. accounted for *** of such total imports from Japan in 1977, *** in 1978, and almost *** in 1979.

Since 1977, * * * landed cost (duty-paid) has been at or above the high end of the low-price range -- * * * per kilo compared with * * * in 1978, and * * * compared with * * * per kilo in 1979. The landed cost to * * * and * * *, * * * and * * * and * * *, respectively, was at the high end of low-price range. Nevertheless, those two brokers together accounted for *** of total imports of dl-cal pan from Japan recorded in the net import file. Brokers rather than trading companies or integrated producers are currently the strongest market force at the low end of the price range.

5. Landed cost of dl-cal pan imports from countries other than Japan.--In 1974-75, importing companies sourcing dl-cal pan from Poland dominate the firms in the lowest one-third of the range of f.o.b. export values of U.S. imports from countries other than Japan (table 9). * * * replaces * * * as the source country of firms in the lowest third of the range in 1976, 1977, and 1979. In 1978, imports of dl-cal pan at low prices from countries other than * * * are sourced almost equally from * * * and from * * *

* * * appears as a significant importer in the group of firms in the lowest one-third of the range of f.o.b. values. * * * share of total imports from countries other than Japan ranged from a low of *** in 1975 to a high of *** in 1977. In 1976 and in 1978, *** does not appear in the lowest third group but enjoyed a share of *** of such imports in each of those respective years. 1/ * * * sources from both Poland and Romania and on occasion (1978) from West Germany. * * *, sourcing from Romania, has become a major low price importer of non-Japanese dl-cal pan. * * *, however, has been the importer with the lowest landed cost, directly, or through a surrogate importer such as * * * in 1978. 2/ The import price trend over the entire period tends to match the business cycle pattern 1974-79, with prices lowest in 1975-76.

6. The landed cost (duty-paid) of d-cal pan to specific importing firms.--Tables 10 and 11, present data calculated from the net import file on the landed costs, by named importer, of those firms in the lowest one-third of the range of f.o.b. export values of U.S. imports of d-cal pan. To gage the relative market impact of such low-priced imports, these data also provide the ratio of a specific firm's imports, by quantities, to the total quantity of imports recorded from Japan in the net import file or from other source countries.

1/ See exhibit N. Included are also data on importers of d-cal pan.
2/ * * *

Table 8.--Dl-calcium pantothenate: U.S. importers' share of total imports from Japan and unit values and selling prices of such imports, 1/ by firms, 1974-79

(Per kilo)

Year and firm	Ratio of firms' imports to total quantity imported	Unit value F.o.b.	Unit value C.i.f. duty 2/	Selling price
	Percent	-----Per kilo-----		
1974:				
***	***	***	***	-
1975	-	-	-	-
1976	-	-	-	-
1977:				
***	***	***	***	-
***	***	***	***	***
***	***	***	***	***
Total	***	-	-	-
1978:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***			
1979:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	***
***	***	***	***	-
*** 3/	***	***	***	-
Total				

1/ Unit values shown are in the lowest 33 percent of the unit value range.

2/ C.i.f. values are estimated from official statistics of the U.S. Department of Commerce. Duty on calcium pantothenate, TSUSA item 437.8225 is 4 percent ad valorem for Japan.

3/ Mitsui was not within the lowest one-third of f.o.b. export values but was included for purposes of comparison.

Source: Compiled from statistics of the U.S. Customs Service.

Table 9.--Dl-calcium pantothenate: U.S. importers' share of total imports from countries other than Japan, unit values, 1/ and selling prices of such imports, by firms, 1974-79

(Per kilo)

Year and firm	Ratio of firm's imports to total quantity imported	Unit value: F.o.b.	Unit value: C.i.f. duty 2/	Selling price
	Percent	-----Per kilo-----		
1974:				
***	*** ***	***	***	-
***	*** ***	***	***	-
Total	*** ***			-
1975:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1976:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1977:				
***	***	***	***	***
***	***	***	***	-
***	***	***	***	***
Total	***	-	-	-
1978:				
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1979:				
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-

1/ Unit values shown are in the lowest 33 percent of the range of unit values.

2/ C.i.f. values were estimated using official statistics of the U.S. Department of Commerce. Column 1 duty rates on calcium pantothenate (TSUSA item 437.8225) are 4 percent ad valorem for countries with MFN status (Japan, United Kingdom, Netherlands, Republic of Korea, Federal Republic of Germany, Switzerland, Spain, Canada, Denmark, Poland, and Italy are sources of pantothenate with MFN status). The column 1 duty rate for Hungary is 25 percent ad valorem. Since 1977, imports from Israel have not been subject to duty because of GSP status. Imports from Romania were subject to a 25-percent ad valorem duty in 1974 and 1975. During 1976, imports from Romania entered at 3 duty rates: (1) 25 percent, (2) 4 percent MFN status, and (3) free of duty because of GSP status. The majority of Romanian imports during 1977 and 1978 entered under GSP status, while the remainder were assessed 4 percent. All Romanian imports entered under GSP status during 1979.

Source: Compiled from statistics of the U.S. Customs Service.

7. Landed cost of imports of d-cal pan sourced from Japan.--Firms in the lowest one-third of the range of f.o.b. export values of U.S. imports of d-cal pan have accounted for an increasing share of such imports from Japan. This group's share of total d-cal pan imports from Japan increased from *** in 1974 to *** in 1975, and has since varied from about *** to *** (table 10).

Although 6 to 10 firms make up the group in the lowest one-third of the low-price range in a given year, since 1975, * * * is the major market force in terms of import share. The landed-cost price of * * * for d-cal pan from Japan usually falls at about midway in the range of low prices. In 1977 * * * was at the low end of the lowest one-third of the imported d-cal pan cost price range with a landed (duty-paid) cost of * * * compared with the highest figure of * * * per kilo paid by * * *. In 1979, * * * import cost price per kilo was * * * compared with a low of * * * for * * * and a high of * * * for * * *.

Since 1975, * * * quantity share in imports of d-cal pan from Japan has been approximately ***, except in 1979, when that figure fell to not quite ***. * * * landed cost prices were not at the low end of this lowest one-third range in any year and were usually proximate to or above the landed cost price of * * *

The range of landed cost prices corresponding to the lowest one-third of the f.o.b. values of U.S. imports of Japanese d-cal pan varied considerably during 1974-79. The spread was about * * * per kilogram in 1974, narrowed to roughly half that amount under the increased competition during the recession of 1975-76, then widened sharply to a spread of about * * * per kilogram between the low and high landed-cost figures during 1978 and 1979.

8. Landed cost of d-cal pan imports from countries other than Japan.-- * * * appears as the low-cost importer of d-cal pan early in the period 1974-76. In the last 3 years, however, * * * has not been among the lowest-landed-cost price importers of d-cal pan from countries other than Japan. During 1974-76, * * * accounted for * * * of such total imports. Although its landed-cost-price in each of the last 2 years (1978-79) was at the mid range or high end of the price spectrum, * * * continued to dominate this segment of d-cal pan import supply. Its share of recorded imports in the net import file was *** in 1978 and *** in 1979. Since the 1975-76 recession, the range of landed-cost-price for imports from countries other than Japan has varied by about *** per kilogram between firms in the lowest one-third of the range of landed-cost-price.

Table 10.--D-calcium pantothenate: U.S. importers' share of total imports from Japan, unit values, 1/ and selling prices of such imports, by firms, 1974-79

(Per kilo)

Year and firm	Ratio of firm's imports to total quantity imported	Unit value		Selling price
		F.o.b.	C.i.f. duty 2/	
	Percent	------Per kilo------		
1974:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1975:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1976:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	***
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1977:				
***	***	***	***	-
***	***	***	***	***
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	73.5	-	-	-

Table 10.--D-calcium pantothenate: U.S. importers' share of total imports from Japan, unit values, 1/ and selling prices of such imports, by firms, 1974-79--Con.

(Per kilo)

Year and firm	Ratio of firm's imports to total quantity imported	Unit value		Selling price
		F.o.b.	C.i.f. duty 2/	
	Percent	-----Per kilo-----		
1978:				
***	***	***	***	-
***	***	***	***	-
***	***	***	***	***
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
Total	***	-	-	-
1979:				
***	***	***	***	***
***	***	***	***	-
***	***	***	***	***
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	-
***	***	***	***	***
Total	***	-	-	-

1/ Unit values shown are in the lowest 33 percent of the range of unit values.

2/ C.i.f. values were estimated using official statistics of the U.S. Department of Commerce. Column 1 duty rates on calcium pantothenate (TSUSA item 437.8225) are 4 percent ad valorem for countries with MFN status (Japan, United Kingdom, Netherlands, Republic of Korea, Federal Republic of Germany, Switzerland, Spain, Canada, Denmark, Poland, and Italy are sources of pantothenate with MFN status). The column 1 duty rate for Hungary is 25 percent ad valorem. Since 1977, imports from Israel have not been subject to duty because of GSP status. Imports from Romania were subject to a 25-percent ad valorem duty in 1974 and 1975. During 1976, imports from Romania entered at 3 duty rates: (1) 25 percent, (2) 4 percent MFN status, and (3) free of duty because of GSP status. The majority of Romanian imports during 1977 and 1978 entered under GSP status, while the remainder were assessed 4 percent. All Romanian imports entered under GSP status during 1979.

Source: Compiled from statistics of the U.S. Customs Service.

Table 11.--D-calcium pantothenate: U.S. importers' share of total imports from countries other than Japan, unit values, 1/ and selling prices of such imports, by firms, 1974-79

(Per kilo)

Year and firm	Ratio of firm's imports to total quantity imported	Unit value		Selling price
		F.o.b.	C.i.f. duty 2/	
	Percent	-----Per kilo-----		
1974:				
*** 3/	***	***	***	-
1975:				
*** 3/	***	***	***	-
1976:				
*** 3/	***	***	***	***
*** 4/	***	***	***	-
Total	***	-	-	-
1977:				
*** 4/	***	***	***	-
*** 4/	***	***	***	-
Total	***	-	-	-
1978:				
*** 5/	***	***	***	-
*** 5/	***	***	***	-
*** 3/	***	***	***	-
Total	***	-	-	-
1979:				
*** 6/	***	***	***	-
*** 5/	***	***	***	-
Total	***	-	-	-

1/ Unit values shown are in the lowest 33 percent of the range of unit values.

2/ C.i.f. values were estimated using official statistics of the U.S. Department of Commerce. Column 1 duty rates on calcium pantothenate (TSUSA item 437.8225) are 4 percent ad valorem for countries with MFN status (Japan, United Kingdom, Netherlands, Republic of Korea, Federal Republic of Germany, Switzerland, Spain, Canada, Denmark, Poland, and Italy are sources of pantothenate with MFN status). The column 1 duty rate for Hungary is 25 percent ad valorem. Since 1977, imports from Israel have not been subject to duty because of GSP status. Imports from Romania were subject to a 25 percent ad valorem duty in 1974 and 1975. During 1976, imports from Romania entered at 3 duty rates: (1) 25 percent, (2) 4 percent MFN status, and (3) free of duty because of GSP status. The majority of Romanian imports during 1977 and 1978 entered under GSP status, while the remainder were assessed 4 percent. All Romanian imports entered under GSP status during 1979.

3/ ***

4/ ***

5/ ***

6/ ***

Source: Compiled from statistics of the U.S. Customs Service.

E. Market prices of cal pan and importers' cost prices

Data on market prices for dl-cal pan and d-cal pan was requested from the three domestic producers. 1/ Several importers were asked to provide data on their cost price of cal pan from Japan and from other source countries and on their selling price of imported cal pan. Records of sales reports containing transaction prices or offer prices of competitors were also requested from domestic producers. Data submitted were meager in some cases and complete in others; broader coverage was received for the period 1977-79 than for earlier years. These data are compiled in table 13, and enable a rough comparison of price trends and competitive price patterns.

1. Prices of dl-cal pan.--The range of market prices compiled from sales reports plus Syntex' typical selling prices provide a transaction price picture for the full period 1974-80. Prices per kilo increased from a low of * * * in 1974 to a high of * * * in 1979. As the animal feed market weakened in 1980, the high end of the price range tumbled to * * * per kilo, representing a decline of about ***. The price effect of the 1975-76 recession is apparent in both Syntex prices and those of Diamond Shamrock which was still producing dl-cal pan in 1975. Market prices in those two years declined about ***. Syntex' prices were *** to *** below the range of prices compiled from sales reports in 1977 and 1979, but were at mid range in 1978 and 1980.

Importers' cost prices reported by * * * 2/ and * * * 3/ are f.o.b. port of origin in Japan. Landed duty-paid cost would add about ***, bringing these prices in line with the range of importers' landed cost prices as calculated from the net import file. Adding a profit margin, which according to importers ranges from *** to as much as ***, depending on the market and import source, would bring the price of imported dl-cal pan well within the range of market prices compiled from sales reports and about *** to *** below Syntex' typical prices.

2. Prices of d-cal pan.--The range of market prices for d-cal pan compiled from sales reports as well as market transaction prices reported by Syntex and Thompson-Hayward confirm a steady, uninterrupted rising price trend from 1976 to 1980. Prices of d-cal pan show little change during 1974-76, remaining at a range of * * * to * * * per kilo. From 1977 to 1980, market prices of d-cal pan per kilo increased from a range of * * *-* * * to * * *-* * *, or by roughly ***. Syntex reports a selling price of * * * per kilo in 1980. * * *

* * * Importers' cost prices (export price f.o.b. port of origin) as reported by * * * and * * *, when adjusted to a landed, duty-paid basis including margin, would * * * reported by Thompson-Hayward but would be *** to *** those of Syntex and the high end of the range of prices compiled from sales reports.

1/ See exhibits O, P, Q, and R.
2/ See exhibits S and T.

Table 12.--Calcium pantothenate: Range of market prices of dl-cal pan and d-cal pan, 1/ typical selling prices of specific firms, importers' f.o.b. cost prices, and importers' average landed cost, 1974-80

Item	1974	1975	1976	1977	1978	1979	1980
	Dl-cal pan (per kilogram)						
Range of market prices compiled from sales reports 1/				***-***	***-***	***-***	***-***
Typical selling prices as reported by Syntex	***	***	***	***	***	***	***
Typical selling prices as reported by Diamond Shamrock	***-***	***-***					
Importers' f.o.b. cost price as reported by ***					3/***-***	2/***-*** 3/***-***	
Importers' f.o.b. cost price as reported by ***					4/ ***	4/ ***	4/ ***
Importers' average landed cost (duty-paid) calculated from the net import file:							
Sourced from Japan	***			***	***	***	
Sourced from other countries	***	***	***	***	***	***	
	D-cal pan (per kilogram)						
Range of market prices compiled from sales reports 1/			***-***	***-***	***-***	***-***	***-***
Typical selling prices as reported by Syntex	***	***	***	***	***	***	***-***
Typical selling prices as reported by Diamond Shamrock	5/ *** 6/ ***-***	6/ ***					
Typical selling prices as reported by Thompson-Hayward			***-***	***-***	***-***	***-***	
Importers' f.o.b. cost price as reported by ***		7/ ***	7/***-***	7/***-*** 8/***-***	7/***-*** 8/***-***	7/***-***	
Importers' f.o.b. cost price as reported by ***		***-***	***-***	***-***	9/***-***	9/***-***	
Importers' average landed cost (duty-paid) calculated from the net import file:							
Sourced from Japan	***	***	***	***	***	***	
Sourced from other countries:	***	***	***	***	***	***	

1/ ***
2/ ***3/*** 4/ ***
5/ *** 6/ *** 7/ *** 8/ ***
9/ ***

Source: Prices compiled from producer and importer responses in Investigation No. 603-5; importers' landed cost prices calculated from the net import file of the U.S. Bureau of Customs.

3. Market price of d-cal pan and dl-cal pan by specific firms.--Table 13 presents a cross-section price analysis of actual transaction price or offer price by specified domestic producers and importers during 1976-80. These prices were compiled from salesmans' reports of calls made on specifically identified cal pan purchaser accounts. The prices are those by named competitors which resulted in lost sales or adjusted offer prices made to meet competitors' prices or to retain an account.

(a) Dl-cal pan market prices.--The identities of competitors were not known in most instances where salesmen recorded import competition. Of the nine firms that were identified, * * *, * * *, and * * * appeared most frequently in the sales reports. Transaction prices usually were delivered prices. Although the importer usually was unknown, dl-cal pan sourced from * * * and * * * was often the lowest priced imported product. For example, * * * sold dl-cal pan sourced from * * * at * * * per kilo gram in 1978.

* * * frequently met import competition at prices that covered the range of market price (1978 and 1980). The typical * * * selling prices reported by that firm were somewhat below the range of * * * prices noted in sales reports to meet import competition in 1977 and 1979. * * * quotes a typical price as * * * per kilogram in 1977, but the range of * * * prices to meet import competition was * * *-* * * per kilogram, as shown in table 13. In 1979, the typical price per kilo as submitted by * * * was * * *, compared with a * * *-* * * price range recorded to meet import competition.

According to available data, * * * prices were among the lowest during the past several years, slightly lower than those of * * * and about *** lower than those of * * *.

b) D-cal pan market prices.--Three firms appear consistently and repeatedly as strong competitors in the d-cal pan market: Thompson-Hayward, Hoffman-LaRoche, and H. Reisman. Competitive prices are clustered in almost identical price ranges between the three firms. No particular one of the three stands out as a price leader on the down side of the price range, except in 1980, when * * * price of d-cal pan was * * * per kilo, compared with prices of * * * to * * * per kilo by * * * and * * *. * * * does not appear in the sales reports as a competitive factor in lost sales in 1979 and 1980 as it did in 1976-78. As many as eight firms, however, are identified in the sales report sample of market competition resulting in lost sales or reduced offer prices to meet competition. The transaction prices of these firms are * * * every year than the typical selling prices reported by Syntex. The margin of underselling of other market competitors compared with that of Syntex ranges from as much as * * * per kilo in 1977 to * * * per kilo in 1980. The price differential and competitive price disadvantage is shown in the following tabulation (in percent):

Item	1976	1977	1978	1979	1980
Typical Syntex price----------	***	***	***	***	***
Range of market prices--------	***	***	***	***	***
Margin of underselling percentage------------------	***	***	***	***	***
Percentage price disadvantages----------------	***	***	***	***	***

The gravamen of Syntex' complaint sounds in a Sherman Act conspiracy to engage in predatory pricing with the intent to completely dominate and take over the cal pan market in the United States. 1/ The purpose of this type of predatory pricing is to sell at a price low enough to drive all of a firm's competitors out of business in the relevant market. Once this objective is achieved, the firm then raises its prices to an artificially high level in order to recoup the losses incurred during the period of below-cost sales. In order to successfully engage in such course of conduct, a firm must have "deep pockets" and an ability to financially withstand large losses, since that firm will also suffer losses for a given period of time as great, if not greater, than the competitors which are the target of the predatory pricing scheme.

The allegation of a conspiracy to restrain trade or to monopolize the cal pan market 2/ is supportable only if the predatory pricing scheme is conducted with cooperation between the manufacturer and its distributors, in this case the named respondents Mitsui and Alps Pharmaceutical. The complaint presents all the classic elements of monopolistic predatory pricing with its corollary maintenance of a monopoly, which is itself a violation of section 2 of the Sherman Act. The named respondents have allegedly taken over a tremendous share of the entire cal pan market in a relatively short time, from a negligible share of the market to 100 percent of d-cal pan submarket and 70 percent of the dl-cal pan submarket. This supposedly has had the effect of eradicating all domestic competition except for Syntex Agribusiness. Having achieved a monopoly in d-cal pan, according to Syntex, the Japanese producers have begun to raise their prices to monopolistic levels, thereby completing the requisite course of conduct necessary to establish violations of sections 1 and 2 of the Sherman Act. On the basis of the factual matter which has been gathered by the Commission staff during its investigation, it is clear that the allegations presented in the complaint are unsupportable.

A. Monopolization under section 2 of the Sherman Act

(1) The relevant market

The relevant product market in issue in this investigation is clearly cal pan, with submarkets in d- and dl-cal pan. 3/ Cal pan, as described previously, has essentially two primary uses--animal nutrition and human vitamin supplements.

1/ Secs. 1 and 2, 15 U.S.C. 1, 2.

2/ A violation of sec. 1 of the Sherman Act.

3/ Cal pan calcium chloride complex is an optional commercial grade of dl-cal pan which is irrelevant for the purpose of the definition of the relevant product market.

VII. Legal analysis

The October 26, 1979, complaint filed by Syntex Agribusiness alleges that Mitsui & Co., Alps Phamaceutical Corp. and their U.S. distributors, importers, 1/ individually or in combination with each other, and other unknown co-conspirators are:

(1) importing and selling cal pan at unreasonably low prices, including sales below average variable cost and below average total cost, the effect or tendency of which is to substantially injure or destroy a United States inudstry, efficiently and economically operated;

(2) engaged in predatory pricing schemes to restrain trade or to monopolize the cal pan market in the United States;

(3) selling cal pan below average variable cost with the intent to restrain trade or to monopolize the U.S. market; and

(4) maintaining a monopoly in a submarket of cal pan, which is d-cal pan.

Syntex has alleged that Japanese manufacturers and their distributors have a complete monopoly in the sale of d-cal pan in the U.S. market because of the eradication of the U.S. industry, and have increased their market share of dl-cal pan from a negligible amount to at least 70 percent in 3 years. 2/ Since the complainant has been realizing only a negligible return on sales of dl-cal pan, and is in danger of being forced out of the market, it is alleged that the named respondents could also have a virtual monopoly in the U.S. dl-cal pan market. 3/

The basic thrust of the complaint is that U.S. manufacturers have been, and are being, forced out of the cal pan market because they cannot compete with the unfair pricing practices of the named respondents. Syntex has allegedly lowered its prices below its total cost in order to keep pace with Japanese prices, but the Japanese producers only respond by further lowering their prices. This pricing behavior is apparently designed not only to eliminate existing competitors, but also to deter the entry into the market of any future competitors. Thus, it would appear that the named respondents would lower their prices whenever entry in the U.S. cal pan market is attempted by a potential competitor.

1/ Alps Pharmaceutical Co. and Mitsui are the only named respondents in the complaint.

2/ Complaint, p. 27.

3/ Ibid. Also see complaint, p. 26.

The three domestic U.S. producers imported * * * kilograms or *** of total imports recorded in the net import file. * * * It is clear that integrated producer operations dominate the import segment of the d-cal pan market.

7. Principal importers of dl-cal pan in 1979.--The major dl-cal pan importers for 1979, by importer types, are shown in the following tabulation:

Importer	Quantity (kilograms)	Value (U.S. dollars)	Source
* * * 1/, 2/	* * *	* * *	* * *
* * * 2/	* * *	* * *	* * *
* * *	* * *	* * *	* * *
* * *	* * *	* * *	* * *
Subtotal	* * *	* * *	
* * *	* * *	* * *	* * *
* * *	* * *	* * *	* * *
Subtotal	* * *	* * *	
Total	* * *	* * *	
Total, net import file	* * *	* * *	

1/ * * *
2/ * * *

Six importers accounted for * * * kilograms of dl-cal pan imports, or *** of total imports recorded in the net import file and the same share based on value. Four importers sourced their imports from Japan, accounting for *** of the total imports recorded in the net import file, while only two importers sourced from Romania, contributing *** of the total imports recorded in the net import file. No domestic producers or foreign producers are among these six importers, all of which are brokers, distributors, or premixers.

6. Principal importers of d-cal pan in 1979.--The major d-cal pan importers for 1979, by importer types, are shown in the following tabulation:

Type of importer	Quantity (kilograms)	Value (U.S. dollars)
Domestic producers:		
* * *	* * *	* * *
* * *	* * *	* * *
* * *	* * *	* * *
Foreign producers:		
* * *	* * *	* * *
* * * 1/	* * *	* * *
Brokers and distributors:		
* * *	* * *	* * *
* * *	* * *	* * *
* * *	* * *	* * *
Subtotal	* * *	* * *
Net import file total 2/	* * *	* * *
Subtotal as percent of total	* * *	* * *

As shown in the preceding tabulation, 8 of 30 importers accounted for * * * kilograms of d-cal pan imports valued at * * *. As a share of total imports recorded in the net import file, these eight importers accounted for ***, by quantity, and ***, by value. All of these imports except * * * kilos of cal pan made in Scotland (Roche Products Inc.) were from Japan.

1/ * * *.
2/ * * *.

VI. Relationship between foreign producers and importers of cal pan

A. The relationship of Alps to Japanese trading companies

* * * * * * *

B. Importers of cal pan

Importers of cal pan include independent brokers and distributors, Japanese trading companies, end-use purchasers such as premixers (both merchant and captive) and pharmaceutical companies, and also domestic producers that supplement their cal pan output or fill out their line with imports. A representative list of these importers is shown in exhibit N. Several typical importers were contacted by the staff, and a brief synoposis of those facts obtained follows.

1. Mitsui & Co. of America, Inc.-- * * * * * * *

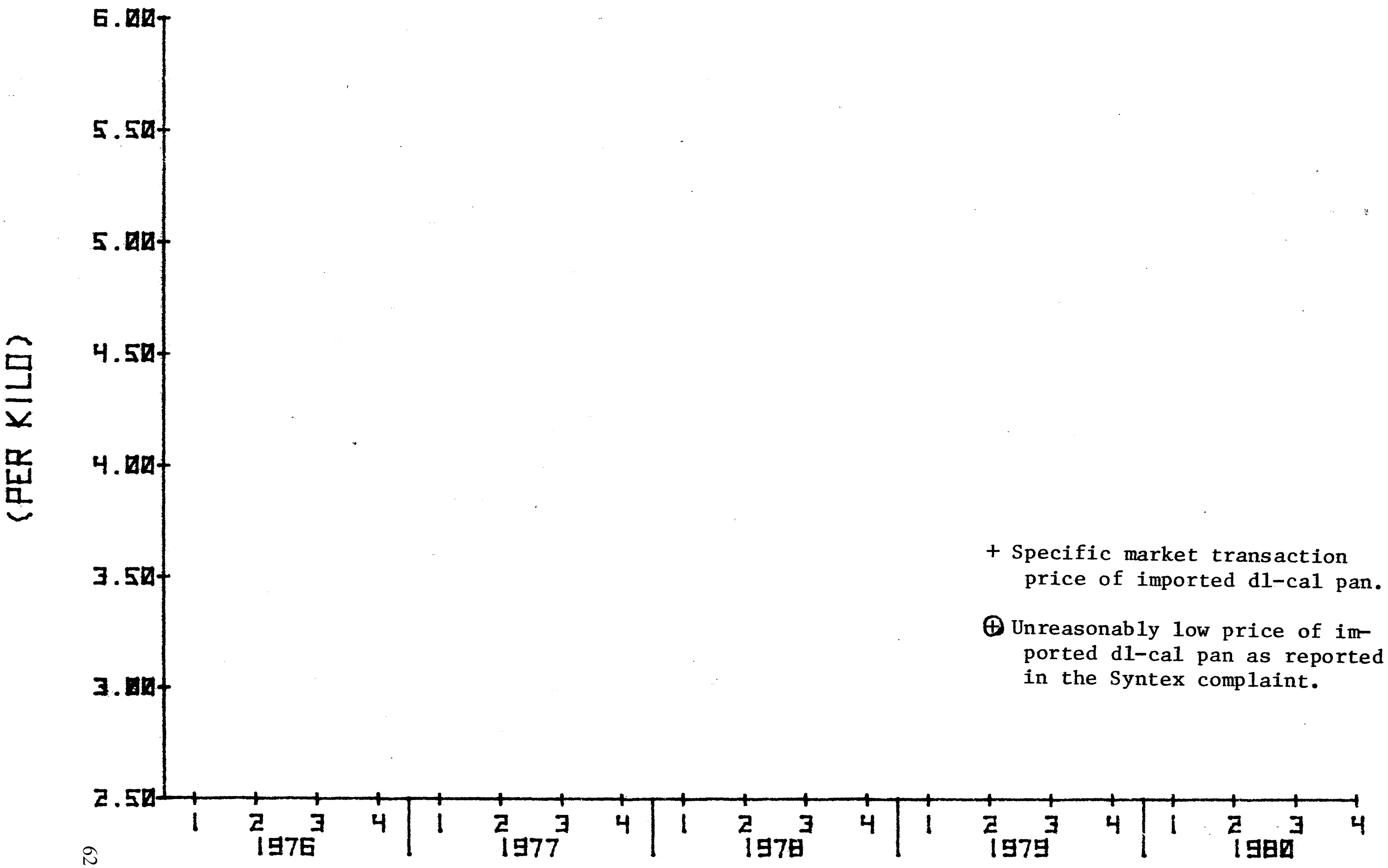
2. Independent brokers and distributors.--This class of importers includes such key firms as * * * These importers source from Japan as well as from Europe and import d-cal pan and dl-cal pan. All have been active importers over the past few years.

3. Pharmaceutical companies.--The only major pharmaceutical firm importing cal pan directly for its own account is * * *. * * * formerly had modest European production facilities for the manufacturing of d-cal pan.

4. Domestic producers.--All three domestic producers import cal pan--* * *

5. Importers sourcing from bloc country producers.--Imports of dl-cal pan which originate from production sources in Poland and Romania are primarily channeled through * * *. Romanian exports of cal pan to the U.S. market also are imported by * * *. * * * imports dl-cal pan from both Poland and Romania. * * * also has imported dl-cal pan from Poland in the past 2 years. Exhibit N lists imports of dl-cal pan for 1974-79 by countries of origin and imports of record. Exhibit N also lists imports of d-cal pan for 1974-79 by countries of origin and importers of record. These two exhibits are based on the net import file of U.S. Customs Service and provide data by importer on quantity, value, and unit value of cal pan imports.

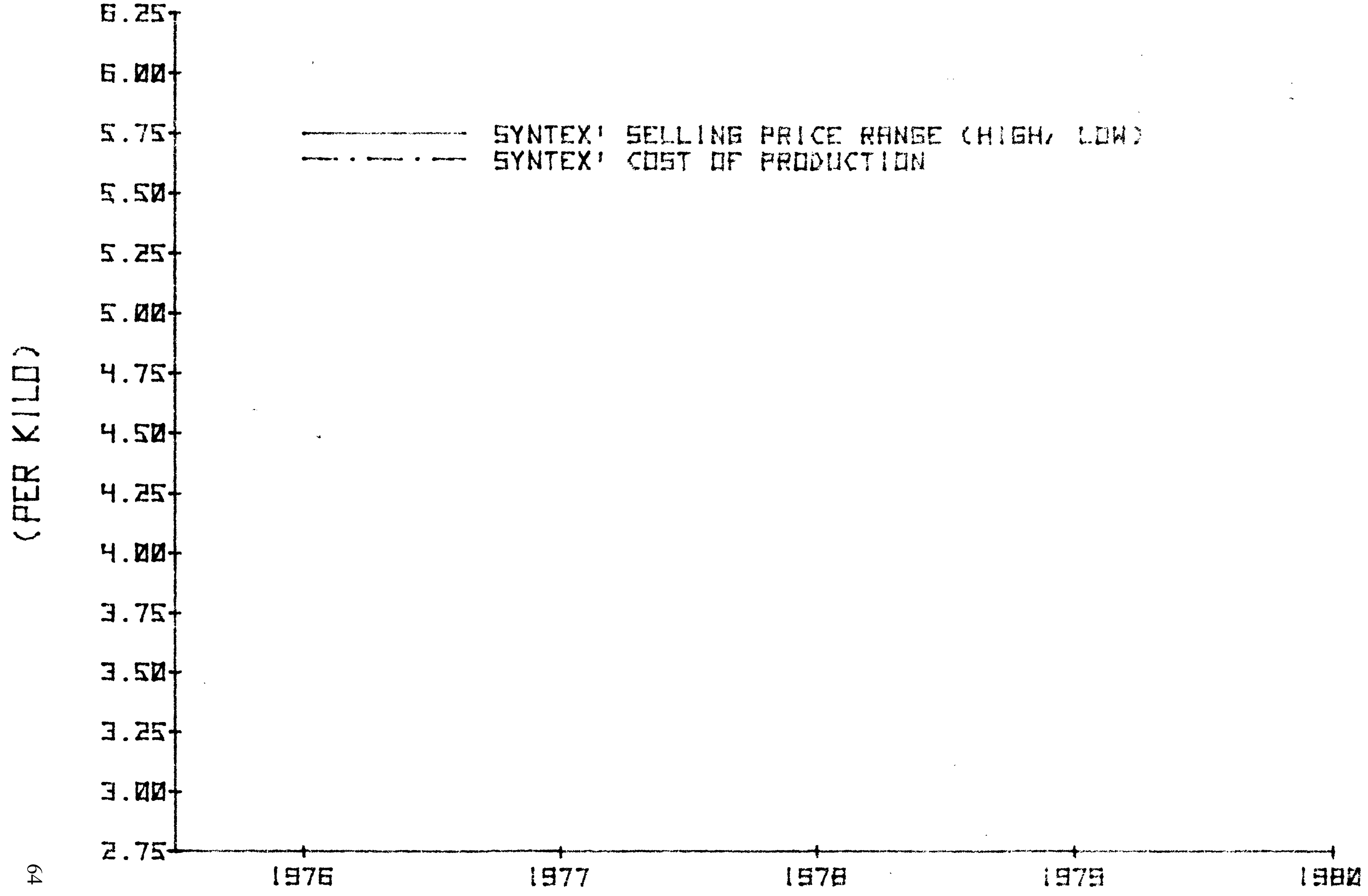
Figure 8.--Dl-calcium pantothenate: Reported market transaction prices of competing imports, by quarters, 1976-79 and January-March 1980.



Source: Compiled from Syntex' sales reports.

The incidence of low pricing is low as indicated by the considerably higher average transaction price of imported material calculated from the sales report data. Figure 8 shows the frequency distribution of the transaction prices of imported dl-cal pan provided by Syntex. In its complaint, Syntex quotes a low price of $3.10 per kilo for dl-cal pan imported from Japan in 1977. The sales reports do not show such a transaction price. Three examples of low prices in the range of * * * to * * * per kilogram are recorded in 1978 sales reports. In one instance, however, the price of * * * to * * * per kilogram is identified as * * * material, f.o.b. Hamburg, in contrast to most of the transaction prices, which are quoted on a delivered basis.

Figure 7.--Dl-calcium pantothenate: Average cost of production and range of selling prices to meet import competition of Syntex, 1976-80.



Source: Based on table 18.

Table 18.--Dl-calcium pantothenate: Syntex' average unit cost of production, range of selling prices to meet import competition, and the ratio of production cost to selling prices, 1976-80

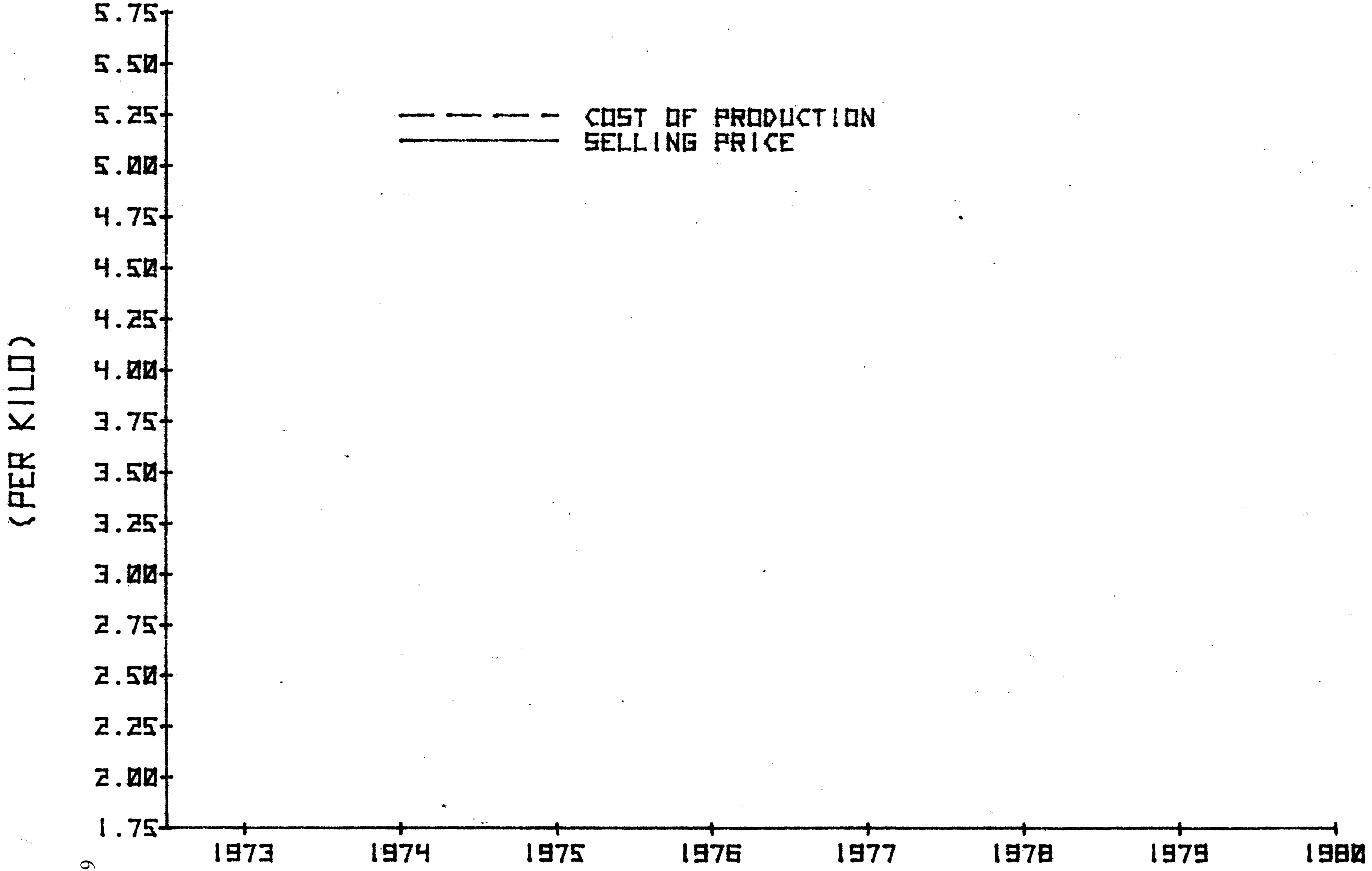
Item	1976	1977	1978	1979	1980
Syntex' average unit cost of production per kilogram-------------------	***	***	***	***	***
Syntex' range of selling prices to meet import competititon 2/ per kilogram-------------------	***-***	***-***	***-***	***-***	***-***
Ratio of production cost to selling price-----------	***-***	***-***	***-***	***-***	***-***

1/ As reported in the Syntex complaint.

2/ Specific transactions in which Syntex saved or made a sale by meeting the import price quote.

Source: Cost of production estimated by U.S. ITC staff from data provided by Syntex; Syntex' prices to meet import competition compiled from sales reports.

Figure 6.--Dl-calcium pantothenate: Average cost of production and average selling price of Syntex, 1973-79.



Source: Based on table 17.

The incidence of low-price is small as indicated by the considerably higher average transaction price of imported material calculated from the sales report data. Figure 8 shows the frequency distribution of the transaction prices of imported dl-cal pan provided by Syntex. In its complaint, Syntex quotes a low-price of $3.10 per kilo for dl-cal pan imported from Japan in 1977. The sales reports do not show such a transaction price. Three examples of low prices in the range of $3.75 to $3.90 per kilogram are recorded in 1978 sales reports. In one instance, however, the price of $3.75 to $3.80 per kilogram is identified as Romanian material, f.o.b. Hamburg, in contrast to most of the transaction prices which are quoted on a delivered basis.

Table 17.--Dl-calcium pantothenate: Syntex' average unit cost of production, and average selling price, and the ratio of production cost to selling price, 1973-80

Item	1973	1974	1975	1976	1977	1978	1979	1980
Syntex' average cost of production per kilogram	***	***	1/***	1/***	***	***	***	***
Syntex' average selling price per kilogram	***	***	***	***	***	***	***	***
Ratio of production cost to selling price---percent	***	***	***	***	***	***	***	***

1/ As reported in the Syntex complaint.

Source: Cost of production estimated by Commission staff from data provided by Syntex; Syntex' average selling prices as reported in the complaint.

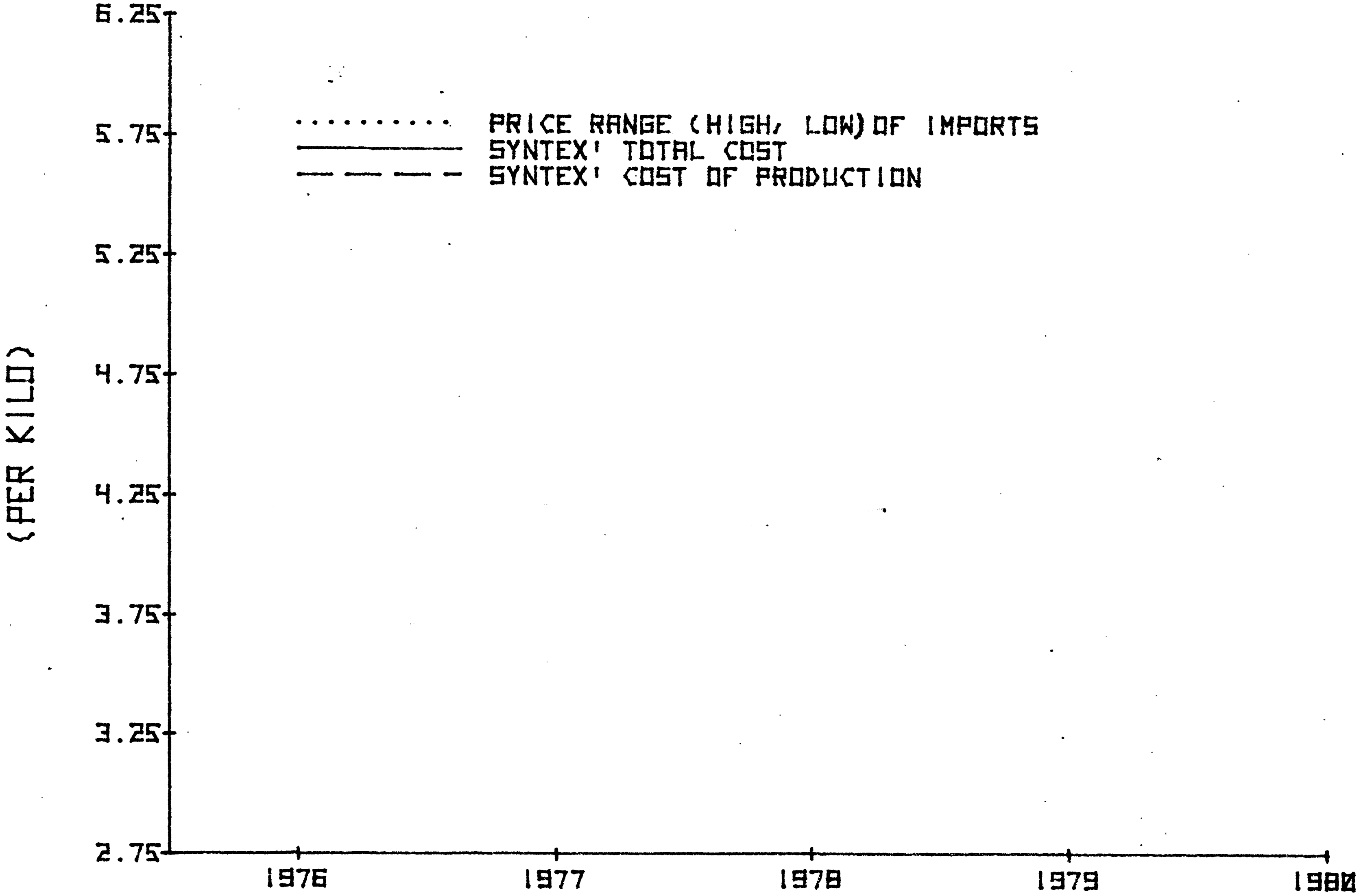
3. Syntex production cost versus its average selling price.--A comparison of the average selling price of Syntex to the firm's average unit cost of production is shown in table 17 and graphically presented in figure 6. Again, only in 1976 did Syntex' average selling price of dl-cal pan fall below (***) its unit cost of production. Over the entire period, however, Syntex's selling price margin has narrowed from roughly *** (1973-75) to an average of about *** (1979-80). Increased competition from * * * and growing numbers of importers and sharply rising costs of production have been contributing factors along with the softening of the cal pan feed grain market in 1979-80.

4. Cost of production versus Syntex prices to meet import competition.-- Syntex provided price data on specific transactions in which the firm met the price of competing imported dl-cal pan. These data are compared with Syntex's average unit cost of production in table 18 and are graphed in figure 7. The data reveal much the same pattern as in the above analysis of import prices and Syntex average selling prices. Syntex met low-priced import competition in 1977 with a range of prices (* * * per kilogram) from *** to *** below its unit cost of production. In each of the following years, however, the firm's selling prices of dl-cal pan were above its unit cost of production, by as much as *** in 1977 or by as slim a margin as *** in 1980. These data on import prices usually do not specify sources in the sales reports on specific transactions. In some cases, the identity of the importer, e.g., ***, indicates a bloc country source. Although some of the low-priced imports of dl-cal pan identified in these sales reports were sourced from Japan, especially in earlier years, or may have been transshipments of Japanese dl-cal pan from Europe, much of the low-priced import pressure appears to have orginated from dl-cal pan sourced from the bloc countries, as previously noted.

In summary, although there have been individual sales of dl-cal pan at below (Syntex) cost of production, on the basis of sales reports of specific transactions, the incidence of such sales has been limited. The following tabulation, on the basis of Syntex' sales reports of specific customer transactions involving import competition, shows the low import price of dl-cal pan and the average price of imported product (per kilogram).

Price	1976	1977	1978	1979	Jan.-Mar. 1980
Lowest -------------------	***	***	***	***	***
Average -----------------	***	***	***	***	***

Figure 5.--Dl-calcium pantothenate: Range of market transaction prices of imports, and average unit cost of production and average total unit cost of Syntex, 1976-80.



Source: Based on table 16.

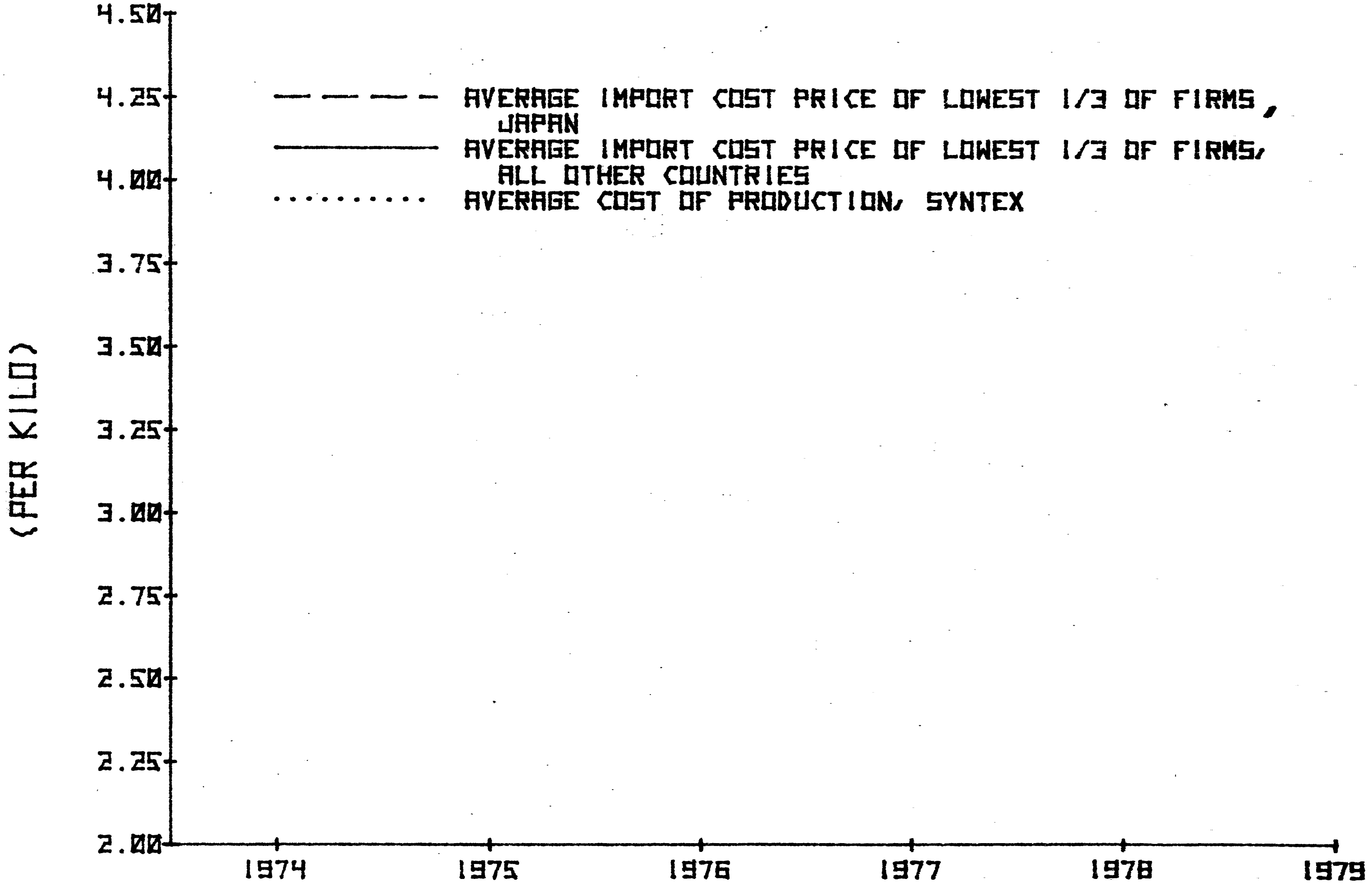
2. Cost of production vesus market transaction prices of imported dl-cal pan.--Table 16 and figure 5 present comparisons of Syntex' cost of production of dl-cal pan and the range of market transaction prices of imported dl-cal pan sold by distributors and/or brokers during 1976-80. In only 1 year, 1976, did the range of prices for imported cal pan approximate or fall below the cost of production of Syntex. The high end of the range was as much as *** above Syntex' cost (1977) and the low end of the range was never closer than *** above Syntex' cost (1979). The ratio of Syntex' total unit cost to transaction price, available for 1976-78, indicates that imports sold at a range of *** to *** below Syntex' total unit costs in 1976 and from *** below to *** above Syntex average' total unit cost in 1978. 1/

Item	1976	1977	1978	1979	1980
Syntex' average cost of production per kilogram	***	***	***	***	***
Syntex' average total cost per kilogram	1/***	1/ ***	1/***	-	-
Range of market transaction prices of imports per kilogram	***- ***	***- ***	***- ***	*** ***	***- ***
Ratio of Syntex' production cost to transaction prices-----percent	***- ***	***- ***	***- ***	***- ***	***- ***
Ratio of Syntex' cost to transaction prices-----percent					

1/ As reported in the Syntex complaint.

Source: Cost of production estimated by Commission staff from data provided by Syntex; market transaction prices of imports compiled from Syntex' sales reports.

Figure 4.--Dl-calcium pantothenate: Average cost of production of Syntex, average cost price 1/ of firms in the lowest 1/3 of the cost price range of imports from Japan and from all other countries, 1974-79.



1/ C.i.f. value plus duty.

Source: Based on table 15.

pattern reflect an average import price (* * * per kilogram) lower than the Syntex cost of production (* * *). This low average price, however, was not for cal pan imported from Japan. Table 15 and figure 4 present similar data for the average import cost price of firms in the lowest one-third of the import price range. Although the margin between the price of cal pan from Japan and Syntex cost of production slims in 1977-79, import cost price remained above production cost by *** in 1977 and 1978 and *** in 1979. In contrast, the cost/price ratio of imports from all other countries shows that the average import prices of non-Japanese cal pan were *** below the Syntex' cost in 1976 and *** and *** lower in 1978 and 1979.

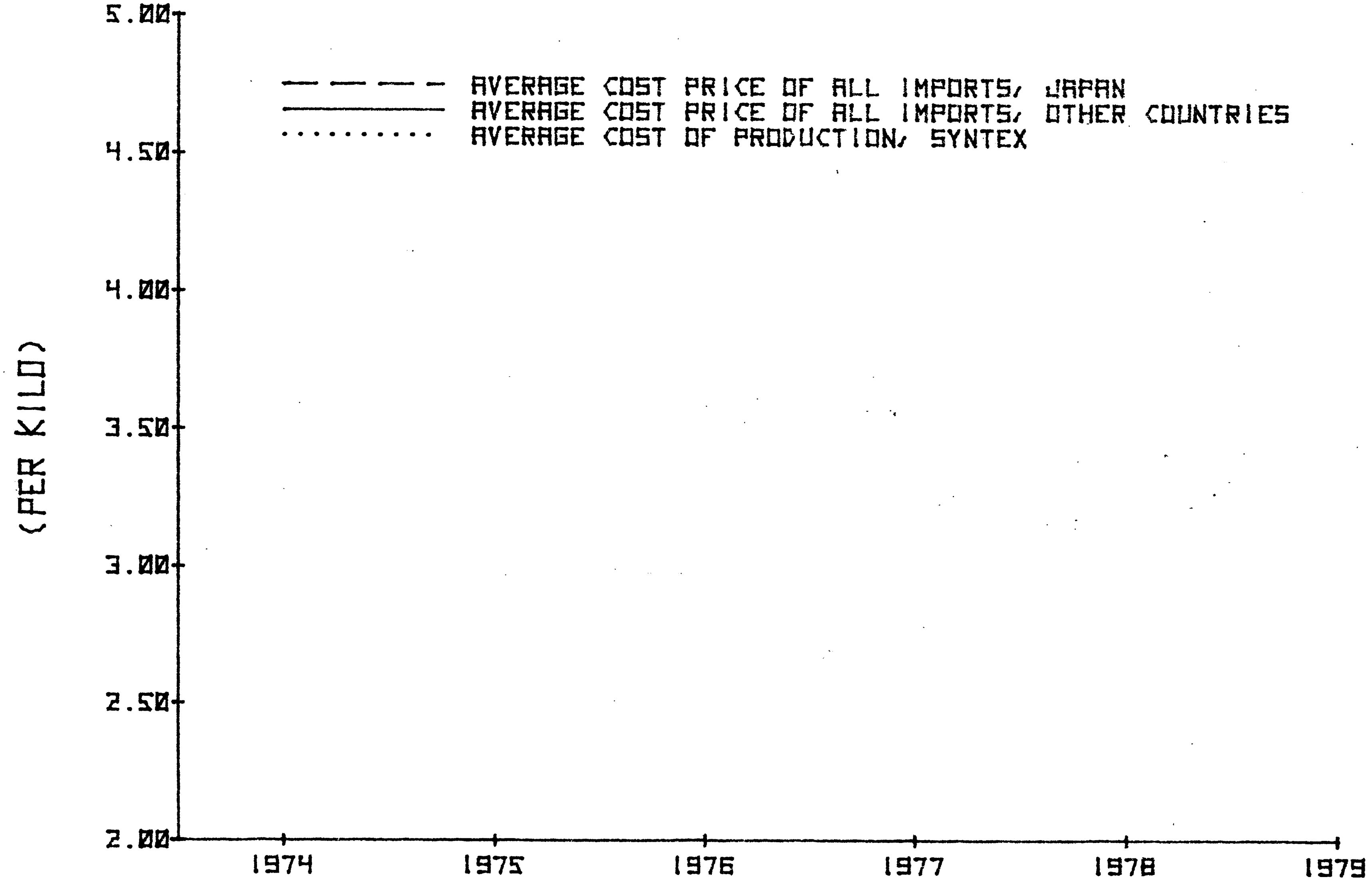
Table 15.--Dl-calcium pantothenate: Syntex' average cost of production, the average cost-price 1/, c.i.f. duty of firm in the lowest 1/3 of the cost-price range of cal pan imports from Japan and from all other countries, the ratio of cost of production to the average cost prices of imports from Japan and ratio of Syntex average production cost to the weighted average cost-price of such imports from all countries, 1974-79

Item	1974	1975	1976	1977	1978	1979
Syntex' average cost per kilogram of production------	***	2/ ***	2/ ***	***	***	***
Weighted average, cost-price per kilogram c.i.f. & duty, of firms in the lowest 1/3 of range of import prices from Japan (per kilogram)--------------	***	-	-	***	***	***
Weighted average cost-price per kilogram c.i.f. & duty, of firms in the lowest 1/3 of range of import prices from all other countries-------------	***	***	***	***	***	***
Ratio of Syntex' weighted average production cost to cost-price of such imports from Japan----------	***	-	-	***	***	***
Ratio of Syntex' average production cost to the weighted average cost-price of such imports from all other countries-------------	***	***	***	***	***	***

1/ C.i.f. plus duty. 2/ As reported in the Syntex complaint.

Source: Cost of production estimated by U.S. ITC staff from data provided by Syntex; cost price of imports from table 12.

Figure 3.--Dl-calcium pantothenate: Average cost of production of Syntex, weighted average cost price 1/ of imports from Japan and all other countries, 1974-79.



1/ C.i.f. value plus duty.

Source: Based on table 14.

processes and problems in the production of cal pan is persuasive to a conclusion that the level of efficiency of Japanese cal pan production is higher than that of U.S. producers and that the Japanese cost of production is lower.

Cost of production versus the cost price of imported dl-cal pan.--The Syntex unit cost of production of dl-cal pan and the average cost price c.i.f. plus duty) of U.S. imports of dl-cal pan from Japan and from all other countries are presented in table 1 and graphically portrayed in figure 3. These data show a ratio of production cost to import prices of dl-cal pan sourced from Japan that narrowed from 0.68 in 1974 to 0.91 in 1979. The ratio of Syntex production cost to the price of imported cal pan from countries other than Japan progressively narrowed from 0.59 in 1977 to 0.99 in 1979.

Table 14.--Dl-calcium pantothenate: Syntex average unit cost of production, and the average cost price 1/ of imports from Japan and from all other countries and the ratio of Syntex cost of production to price of imports from Japan and from all other countries, 1974-79

Item	1974	1975	1976	1977	1978	1979
Syntex' average unit cost of production(per kilogram)------------------	***	2/ ***	2/ ***	***	***	***
Weighted average, cost-price 1/ of imports from Japan (per kilogram)-------	***	-	-	3/***	3/***	***
Weighted average cost price 1/ of imports from all other countries (dollars per kilogram)-----	***	***	3/ ***	3/***	3/***	***
Ratio of Syntex' production cost to cost price 1/ of imports from Japan------percent---------	***	-	-	***	***	***
Ratio of Syntex' production cost to cost-price 1/ of imports from other countries-----percent----------	***	***	***	***	***	***

1/ C.i.f. plus duty.
2/ As reported in the Syntex complaint.
3/ Syntex estimates distributor charges of ( ) percent over and above c.i.f. duty-paid cost are reflected in resale prices of imported cal pan.

Source: Cost of production estimated by U.S. ITC staff from data provided by Syntex; cost price of imports from table 12, this report.

F. Sales below cost

One of the basic questions in this preliminary investigation involves the relative levels of the unit cost of production of dl-cal pan in Japan and the price of U.S. imports of that product from Japan. The complaint alleges that dl-cal pan from Japan was sold at less than total Japanese costs. To support this contention, the complaint presented data on low-priced sales of dl-cal pan in each of the years 1976-78 and by imputing Japanese costs that such sales were at prices less than average variable costs of production in Japan.

Resolving the question of alleged unreasonably low pricing of dl-cal pan imported from Japan would require a comparison of the unit cost of production of Alps Pharmaceutical Co., sole purchaser of dl-cal pan in Japan 1/, to the prices of that product imported into the United States. It would also require analysis of the incidence of the alleged unreasonably low pricing. During this preliminary investigation, it was not possible to obtain data on Alps' cost of production for dl-cal pan. 2/ Syntex did provide their unit cost of production data for dl-cal pan. Thus, it is possible to analyze costs versus prices of dl-cal pan in terms of both import prices and competing domestic prices.

Logic dictates that Japanese unit cost of production of dl-cal pan is, at most, no higher than that of Syntex and, more probably, is appreciably lower than the Syntex unit cost of producing that product. Information provided by Daiichi on the Japanese cal pan production processes, techniques, and productivity, together with the Commission staff 's observance of domestic U.S. plant processes and problems in the production of cal pan, leads to a conclusion that the level of efficiency of Japanese cal pan production is higher than that of U.S. producers and that the Japanese cost of production is lower.

1. Cost of production versus the cost price of imported dl-cal pan.--The Syntex unit cost of production of dl-cal pan and the average cost price c.i.f. plus duty) of U.S. imports of dl-cal pan from Japan and from all other countries are presented in table 14, and graphically portrayed in figure 3. These data show a ratio of production cost to import prices of dl-cal pan sourced from Japan that narrowed from *** in 1974 to *** in 1979. The ratio of the Syntex production cost to the price of imported cal pan from countries other than Japan progressively narrowed from *** in 1977 to *** in 1979. Only in 1976 does the

---

1/ Daiichi, ceased production of dl-cal pan in 1976.

2/ Commission staff efforts to obtain Japanese cost and profit data voluntarily were successful only with respect to Daiichi. This firm, which produces only d-cal pan, provided aggregate benchmark figures on costs and profit. Daiichi stated that little is known about Alps' process or costs.

Table 13.--D and dl calcium pantothenate: Reported transaction prices and yearly range of selling prices of U.S. producers and importers, by firms, 1976-1980

(Per Kilo)

ITEM	1976	1977	1978	1979	1980
			Dl-calcium pantothenate		
***	--	***-***	***	--	--
***	--	***	--	--	--
***	--	***	***	--	***
***	--	***	--	--	--
***	--	--	***	***-***	--
***	--	--	***	--	--
***	--	***-***	***-***	***-***	***
***	--	--	***	--	--
***	--	--	***	***	***
Dl-cal pan range	--	***-***	***-***	***-***	***-***
Typical actual selling prices reported by Syntex	***	***	***	***	***
Syntex price to meet import competition	--	***-***	***-***	***-***	***-***
			D calcium pantothenate		
***	***	***-***	***-***	***-***	***-***
***	***-***	***	***-***	***-***	***
***	--	--	***	***	--
***	--	--	--	***	--
***	--	--	***	***-***	***
***	--	***	--	***-***	--
***	--	--	--	***-***	--
***	--	--	--	--	***
***	***	--	***	--	--
***	***	--	***	--	--
***	***-***	***	***	--	--
***	--	--	***	--	--
D-cal pan range 1/	***-***	***-***	***-***	***-***	***-***
Domestic industry survey of competitive market price 2/	***-***	***-***	***-***	***-***	--
Typical selling prices reported by Syntex	***	***	***	***	***-***

1/ Compiled from sales reports of Syntex and Thompson-Hayward.

2/ Competitive market price compiled by Thompson-Hayward.

Source: Compiled from producer responses.

There are two uses in the d-cal pan submarket, which are U.S.P. d-cal pan, for human vitamins, and a major demand for animal feed grade d-cal pan. Dl-cal pan is used exclusively as a nutritional supplement in animal feed. U.S.P. d-cal pan is purchased almost exclusively by the major pharmaceutical firms which produce human multivitamins. 1/ Feed grade d-cal pan and dl-cal pan 2/ are consumed by premixers of vitamin supplements (both captive and independent) and feed mills which actually blend vitamin supplements in with poultry and swine feeds. Because of the widespread dispersion of the purchasers of cal pan in general, there are no particular geographic submarkets. Thus, the area of effective competition can be said to be the continental United States.

(2) Power in the relevant market

* * * * * * *

As a general proposition, a market share of less than 75 percent will not confer sufficient market power upon a firm whereby it can be deemed to be a monopolistic force in the relevant market. 3/ An analysis of the d-cal pan submarket for 1976-79 discloses * * *. Daiichi's market shares are as follows:

1976------------------- * * *
1977------------------- * * *
1978------------------- * * *
1979------------------- * * *

As previously discussed in section III of this report, the d-cal pan market is shared by several competitors, some of which are relatively new domestic entrants. 4/ Information acquired through interviews establishes that those companies that ceased production of cal pan in 1975 did so primarily because of environmental problems which required the construction of prohibitively expensive new plants and the use of new technologies which were unavailable at the time. Since the cost of imported cal pan was reasonable, these companies decided to cease production, and to supply their customer and own needs by purchasing d and dl-cal pan from foreign and domestic producers. Recently, however, two producers, Diamond Shamrock and Thompson-Hayward, re-entered the relevant market after acquiring new technology and began construction of state-of-the-art production facilities. It is worthwhile at this point to consider a serious omission in the Syntex complaint. On page 14, Syntex states that

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1/ Ninety-six percent biologically active cal pan in the form of pantothenic acid is used in some human cosmetics.

2/ Dl-cal pan is also used, to a minor degree, in pet foods.

3/ U.S. v. United Shoe Machinery, 110 F. Supp. 295, aff'd per curiam, 347 U.S. 521 (1954).

4/ Diamond Shamrock and Daitom (Thompson-Hayward).

since 1975, when it ceased production of d-cal pan, there have been no domestic producers of d-cal pan. This is obviously erroneous in view of the combined 1,200-metric-ton capacity of the Diamond Shamrock and Daitom plants, which exclusively manufacture d-cal pan pursuant to new and patented technologies.

* * * While Daiichi has what may fairly be termed a monopoly in the U.S. d-cal pan submarket, it should be viewed as a "technological" monopoly. 1/ This is because its patented technology represents the state of the art in the production and synthesis of d-cal pan. Thus, during 1976-79, it was virtually the only possible supplier of d-cal pan which would fulfill U.S. demand. The reason for the marked increase in Japanese import penetration was that Japanese d-cal pan was practically the only d-cal pan available in the U.S. market, if not in the world market. As a result of satisfying this demand, the level of penetration grew correspondingly.

As previously stated, the domestic producers of cal pan were forced out of the production of cal pan by reason of insurmountable environmental problems and their attendant financial consequences. This was precisely the reason why Syntex had to cease the production of d-cal pan. 2/ Furthermore, the technology used by Syntex in the synthesis of d-cal pan, used since the late 1940's, had become, for all practical purposes, obsolete. Those events, and not price competition from Japanese d-cal pan, coalesced to create the critical factors which caused Syntex to cease the production of d-cal pan.

This void in the U.S. market necessitated an increased presence by Daiichi in order to meet demand for d-cal pan. Daiichi supplied all purchasers, 3/ including Syntex 4/, with reasonably priced d-cal pan. Thus, the above circumstances combined to give Daiichi the overwhelming market share in the U.S. d-cal pan submarket. This market share provided Daiichi with a monopoly which, as is explained below, is expected to be only temporary.

The re-entry of Diamond Shamrock and Daitom into the d-cal pan submarket has begun to erode Daiichi's market share. * * *

1/ An analogy may be made to IBM or Xerox at the time these companies had the only technology in their given fields, thereby necessarily giving them monopolies.

2/ It will be noted that Celanese Corp. ceased production of a carcinogenic basic raw material purchased at a very low price by Syntex.

3/ * * *

4/ * * *

Such entry into the d-cal pan submarket is antithetical to the presence of an anticompetitive monopoly, as well as monopolistic pricing. An examination of the pricing data compiled by the Commission staff 1/ provides no indication of artificial raising of prices of d-cal pan by Daiichi in order to recoup losses it sustained during its attainment of a significant market share. Rather, the price of d-cal pan in the U.S. has increased only gradually, and according to the complaints of Diamond Shamrock and Daitom, has not as of yet risen to the level they would like to see. Furthermore, Daiichi did not engage in any exclusionary pricing practices upon the re-entry of Diamond Shamrock and Daitom by immediately lowering its price of d-cal pan to a level which would have discouraged the new entrants. This behavior by Daiichi on the entry of new competitors underscores an absence of anticompetitive behavior. The same may also be said with respect to the increased presence of Hoffman-LaRoche in the d-cal pan submarket. As a practical matter, it is the staff's estimate that Daiichi's market share of the d-cal pan submarket is rapidly eroding and should stabilize between *** to *** by 1981.

The maximum market shares held by Alps Pharmaceutical in the dl-cal pan submarket are as follows: 2/

1977-------------------- ***
1978-------------------- ***
1979-------------------- ***

The foregoing sections in this report on the structure of the dl-cal pan submarket and the conditions of competition in that market disclose a plethora of producing competitors located in Japan, the United States, and Eastern bloc countries. The market shares set forth above clearly demonstrate the absence of any monopoly held by Alps, which is the sole Japanese producer of dl-cal pan. Moreover, there is no evidence 3/ that Alps is guilty of an attempt to monopolize, within the meaning of section 2 of the Sherman Act, the dl-cal pan submarket. The Commission staff believes that submarket, as well as that of d-cal pan, to be the subject of healthy and vigorous competition.

1/ See tables 5 and 11, pp. 45, 56.

2/ Reliable dl-cal pan import data for 1975-1976 are unavailable.

3/ Officers of Syntex had no evidence, of even the most circumstantial nature, which would indicate anticompetitive conduct by Japanese producers in the d-cal pan and dl-cal pan submarkets.

(3) *Predatory Pricing*

Predatory pricing involves three elements: unfair pricing practices, intent to eliminate or discipline a competitor, and injury to competition. As a practical matter, to engage in predatory pricing, it is necessary that the predator have a "deep pocket." This "deep pocket" can exist if the predator has sufficient market power in geographic and/or product markets other than the market(s) in which the predator intends to eliminate or discipline another competitor. Predatory pricing can fall within the proscriptions of section 2 of the Sherman Act (15 U.S.C. 2), section 3 of the Robinson-Patman Act (15 U.S.C. 13a) and section 2(a) of the Clayton Act, as amended by the Robinson-Patman Act, 49 Stat. 15-26 (15 U.S.C. 13 (a)). *Hanson* v. *Shell Oil Co.*, 1/ 541 F.2d 1352 (9th Cir. 1976); *International Air Industries* v. *American Excelsior Co.*, 2/ 517 F.2d 714 (5th Cir. 1975), *cert. den.*, 424 U.S. 934 (1976). *Pacific Engineering and Production Co. of Nevada* v. *Kerr-McGee Corp.*, 3/ 551 F.2d 790 (10th Cir. 1977); *U.S.* v. *National Dairy Product Corp.*, 4/ 372 U.S. 29 (1963); *Utah Pie Co.* v. *Continental Baking Co.*, 5/ 386 U.S. 685 (1967); *FTC* v. *Anheuser-Busch, Inc.*, 6/ 363 U.S. 536 (1960); *Anheuser-Busch* v. *FTC*, 7/ 289 F.2d 835 (7th Cir. 1961); *E.B. Muller & Co.* v. *FTC*, 8/ 142 F.2d 511 (6th Cir. 1944); *Moore* v. *Mead's Fine Bread Co.*, 9/ 384 U.S. 115 (1954); *Puerto Rican American Tobacco Co.* v. *American Tobacco Co.*, 10/ 30 F.2d 234 (2nd Cir. 1929), *cert. den.*, 279 U.S. 858 (1929); *Standard Oil Co. of New Jersey* v. *U.S.*, 11/ 221 U.S. 1 (1911). *American Tobacco* v. *U.S.*, 12/ 328 U.S. 781 (1946); *see also*, *Chillicothe Sand and Gravel Co.* v. *Martin Marietta Corp.*, 13/ No. 79-1929 (7th Cir. 1980), comment in BNA, Antitrust and Trade Reg. Rep., No. 949, at 1415 (January 31, 1980). Predatory pricing has been condemned under section 337. *Certain Welded Stainless Steel Pipe and Tube*, USITC Pub. 863 at 17-34, 35-39.

As previously stated, the complaint alleges a classic Sherman Act predatory pricing scheme, as opposed to a Robinson-Patman type of predatory pricing (15 U.S.C. 13(a)).

1/ 15 U.S.C. 2.
2/ 15 U.S.C. 2, 13(a).
3/ 15 U.S.C. 2, 13(a).
4/ 15 U.S.C. 13(a).
5/ 15 U.S.C. 13(a).
6/ 15 U.S.C. 13(a).
7/ Id.
8/ 15 U.S.C. 13(a).
9/ 15 U.S.C. 13(a).
10/ 15 U.S.C. 13(a).
11/ 15 U.S.C. 2.
12/ 15 U.S.C. 2.
13/ 15 U.S.C. 2.

In order to prove predatory pricing, it must be shown that the predator is pricing so unreasonably in the relevant market that one can infer both the predatory intent and injury to competition. Certainly, sales below average variable costs would constitute such unreasonable pricing in most cases. 1/ However, predatory pricing can also be proven without relying on the "double inference test" founded on sales below average variable costs. In order to do this, the complainant must show (1) unreasonably low prices, and (2) predatory intent and injury to competition. Predatory intent can be shown by proof of behavior and/or statements that show that the pricing behavior of the predator is intended to eliminate his competitor. Injury to competition may also be proven by showing that the predator has achieved or will achieve sufficient market power to control pricing in the relevant market (i.e., he can now or will shortly be able to raise his prices to recoup the losses incurred in pursuing his predatory pricing scheme. 2/

The economic data which have been compiled and analyzed by the Commission staff clearly demonstrate that Japanese producers, distributors, and importers of both d- and dl-cal pan are not engaged in predatory pricing. While actual costs of production were not received from the Japanese manufacturers (Fuji/Daiichi, and Alps Pharmaceutical), the selling prices of Japanese d- and dl-cal pan do not provide any indicia of below-average variable, marginal, or total cost sales. Utilizing Syntex' cost of production data for d- and dl-cal pan would bring about distorted results for the reasons that Syntex does not produce d-cal pan in the first place, nor does it produce the basic raw material beta-alanine, which is indispensable to the synthesis of all cal pan. Also, the Syntex data only provide Syntex' theoretical cost of production data for beta-alanine, * * *. The Commission staff has constructed its own view of the Japanese costs for beta-alanine (table 5). Data in this table, when compared with prices of imported cal pan, show that sales of imported cal pan (whether of d-cal pan or dl-cal pan) have not taken place below total cost, below-average variable cost, or below marginal cost.

1/ Hanson v. Shell, supra at 1358; International Air, supra, at 721-725; Pacific Engineering, supra at 797.

2/ In the case cited supra, predatory pricing was found or not found on the basis outlined above. In other words, the double inference test was either supplemented with other evidence implying predatory intent and injury or this other evidence made the use of such test almost unnecessary or it was not used. In Pacific Engineering, the court refused to find predatory pricing based solely on below-average cost sales. See also, Chillicothe Sand and Gravel, supra. In the Muller case, the court found evidence of predatory intent on the basis of factors which are not present in this investigation.

Syntex has alleged 1/ that it is impossible for any company producing d- or dl-cal pan, with the world price of oil fixed at certain rates and with oil more expensive in Japan than in the United States, 2/ to be that much more efficient than Syntex. However, the Commission staff's investigatory activities have disclosed critical flaws in Syntex' contentions. The most significant factor is that while there is an oligopoly in Japan with respect to cal pan producers, there is a rational business logic behind this structure. Since the production of d- and dl-cal pan are perceived in Japan to be two separate fields of endeavor, certain Japanese chemical manufacturers have opted for rationalized production. Thus, Alps Pharmaceutical has specialized in producing mostly dl-cal pan because it is the most efficient producer of this particular product. Likewise, Fuji (using Daiichi technology), has concentrated on, and specialized in, the manufacture of d-cal pan.

The background history on the U.S. cal pan market clearly manifests the serious environmental problems encountered by U.S. producers in the synthesis of cal pan itself, as well as in the use of the raw materials used in the manufacturing processes. These environmental problems, more than any other single factor, appear to have contributed to the domestic producers' inability to profitably manufacture d- and dl-cal pan. 3/ While Japan has equal, if not more strict, environmental safeguards, these requirements are considerably relaxed in rural areas. Both Alps and Fuji are located well away from urban population centers in order to avoid the possible problems encountered by Daiichi's cal pan manufacturing plant. 4/

The data gathered by the Commission staff also disclose the technological superiority of the Japanese in the production of both d- and dl-cal pan. This necessarily leads to optimum efficiency, which in turn leads to lower costs and lower selling prices. The best example of this efficiency is the Daiichi technology used by Fuji (and Daitom in the United States) in the manufacturing of d-cal pan. That process is able to recycle by-products in the process so efficiently as to

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1/ Complaint, p. 24.

2/ Cal pan is a derivative of by-products of petroleum. One of these petrochemical by-products is beta-alanine.

3/ Syntex had been producing beta-alanine (a basic raw material used in the synthesis of cal pan) on a very cost competitive basis until the early to mid 1970's. However, a necessary material for the production of beta-alanine was found to be a patent carcinogen and Syntex' supplier, Celanese Corp., ceased supplying it to Syntex. This was a serious blow to Syntex' production process as it had received this material from Celanese at a very low price.

4/ It is noted in this report that the Tokyo municipal government required Daiichi to cease its operations due to the proximity of the plant to the city.

significantly increase the yield of pure d-cal pan. The staff has been unable to secure data with respect to the production of dl-cal pan by Alps. However, since Alps specializes in dl-cal pan, and manufacturers at least beta-alanine, it would not be unreasonable to assume that Alps has a large efficiency advantage over Syntex.

While it may be argued that the Japanese producers, Fuji/Daiichi and Alps Pharmaceutical, have the necessary "deep pockets" which would enable them to sustain long-term losses in the sale of d- and dl-cal pan in the U.S. market, other necessary factors needed to demonstrate a dangerous probability of success of monopolizing the relevant market are absent. The market share trends discussed previously indicate the erosion of Daiichi's dominance of the U.S. d-cal pan market. Also, there is evidence to establish that there is a growing consumer preference for d-cal pan, as opposed to dl-cal pan. Thus, while Alps may have a healthy share of the dl-cal pan market currently, the trend towards the use of d-cal pan will likewise erode that market share due to less potential sales of dl-cal pan in the U.S. market.

B. Restraint of trade or commerce and/or injury to the domestic industry

(1) Combination and conspiracy

As indicated supra, as well as in the preliminary report submitted to the Commission, [1] the staff has found no evidence of even the most circumstantial nature which would establish the existence of a combination and conspiracy between Japanese producers and distributors to restrain trade in the relevant market. * * * No U.S. firm, including Syntex, nor any individual has any information from which one could be led to believe that there is any cooperation between the Japanese producers and distributors in the U.S. market. By the same token, there is no evidence which would establish a scheme by the Japanese producers and their distributors to absorb any dumping duties. [2]

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[1] June 19, 1980.

[2] Syntex' complaint alleged that large dumping margins were assessed against Daiichi. However, these duties were lowered to miniscule amounts. Moreover, the dumping assessment lapsed on June 13, 1980, by order of the International Trade Administration.

(2) Restraint of trade or commerce

A restraint of trade or commerce means behavior which forecloses substantial competition, either existing or potential, or which tends to create a monopoly. Standard Oil of New Jersey v. U.S., 221 U.S. 1 (1911). Injury to competition is the focal point, and not injury to a single competitor. Klor's v. Broadway-Hale Stores, Inc., 359 U.S. 207 (1959). The data analyzed by the staff discloses that there has been no evidence of anticompetitive behavior by the Japanese producers of d- and dl-cal pan in the U.S. relevant submarkets. The evidence demonstrates that there is presently substantial competition in both of these submarkets.

(3) Injury to the domestic industry

There is no anticompetitive behavior by Daiichi/Fuji, Mitsui, Alps, or others, in the d- and dl-cal pan submarkets in the United States. There are, thus, no unfair acts and unfair methods of competition within the meaning of section 337. Accordingly, there can be no effect or tendency to substantially injure or destroy a domestic industry.

9/19/78 XR 4,115,443

United States Patent [19]

Schmidt et al.

[11] 4,115,443

[45] Sep. 19, 1978

[54] **PROCESS OF MAKING D,L-LITHIUM PANTOATE AND RESOLVING THE RACEMIC MIXTURE INTO ITS OPTICALLY ACTIVE ISOMERS**

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[73] Assignee: Veb Jenapharm, Jena, Democratic Rep. of Germany

[21] Appl. No.: **670,437**

[22] Filed: **Mar. 25, 1976**

Related U.S. Application Data

[60] Continuation of Ser. No. 540,249, Jan. 10, 1975, abandoned, which is a division of Ser. No. 407,254, Oct. 17, 1973, abandoned.

[51] **Int. Cl.**^{2} **C07C 59/04**

[52] **U.S. Cl.** **562/402;** 260/343.6; 562/579

[58] **Field of Search** .... 260/535 R, 343.6

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Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Michael J. Striker

[57] **ABSTRACT**

A process for the resolution of optical isomers of racemic lithium pantoate by selective crystallization from a solution in methanol, ethanol, or other polar solvents, or by electrostatic separation. The optical isomers can be readily converted to optically active pantolactones which are the starting material for the preparation of optically active pantothenic acid and its salt and pantothenyl alcohol. One of the two optical isomers of each of these compounds possesses vitamin activity. The unwanted or inactive optical isomer of lithium pantoate as such is thermally stable and can be racemized by heating in the presence of a basic reacting compound at a temperature between 120 and 180° C to produce a racemic mixture which can then be subjected directly to resolution without conversion to some other derivative in accordance with the processes of the present invention to produce the desired or active optical isomer.

4 Claims, No Drawings

EXHIBIT B

PROCESS OF MAKING D,L-LITHIUM PANTOATE AND RESOLVING THE RACEMIC MIXTURE INTO ITS OPTICALLY ACTIVE ISOMERS

This is a continuation of application Ser. No. 540,249, filed Jan. 10, 1975, now abandoned, which is a div. of Ser. No. 407,254, filed Oct. 17, 1973, now abandoned.

BACKGROUND OF THE INVENTION

The present invention pertains to processes for the resolution of optical isomers of lithium pantoate without the use of optically active resolving agents.

Pantolactone is used for the production of pantothenyl alcohol, pantothenic acid and its salts, such as, for example, calcium pantothenate, which possess vitamin activity and are useful as vitamins. Since such biological activity as vitamins is exhibited only by D(+) isomers, a method is required for resolving racemic mixtures of pantolactone. The resolution can be effected either with pantolactone itself or with calcium pantothenate.

Of the many conventional methods for the resolution of optical isomers, such as adsorption, distillation, use of resolving agents, enzymatic or microbiological separation, conversion to diastereoisomeric pairs of salts, selective or preferential crystallization, and electrostatic separation, the only methods that have been found heretofore to be suitable for the resolution of optical isomers of pantolactone were the use of diastereoisomeric pairs of salts or preferential crystallization of ammonium pantoate which latter method is described, for example, in U.S. Pat. No. 3,529,022. Optical isomers of calcium pantothenate can also be resolved by preferential crystallization.

For separation by formation of pairs of diastereoisomeric salts, the process consists generally either in conversion of the racemic mixture of pantolactones with a suitable optically active base, or conversion of a metal salt of the racemic mixture of pantolactone with a salt of an optically active base and a strong acid. This conversion is effected generally in an alcoholic, aqueous alcoholic, or aqueous medium. There is thus obtained a salt of an optically active isomer having a degree of purity that is dependent upon the solvent and the base used. The corresponding enantiomorphs remain in the mother liquor. The salt and the mother liquor are then separated and the salt is treated in such manner that, after addition of acid, the desired optical isomer of pantolactone is isolated and the base is recovered. The unwanted optically inactive isomer of pantolactone is racemized and the racemic mixture is again resolved to obtain the desired optical isomer.

Optically active bases that were used heretofore included naturally occurring alkaloids such as quinine and ephedrine as well as synthetic optically active compounds such as L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol. Of the synthetic optically active compounds, β-phenylethylamine and dehydroabietylamine are also of importance.

Another method of resolving DL-pantolactones which is described in U.S. Pat. No. 2,383,524 depends upon the use of anhydrides of diacyl-D-tartaric acids, with which the pantolactone is esterified. Pyridine salts of the racemic esters are then formed and, because of their differences in solubility in benzene, the optical isomers are then separated from each other.

For separating racemic pantolactone into its optical isomers by means of preferential crystallization, the racemic mixture is converted into the corresponding ammonium salt and the differences in solubilities of the D and L-ammonium pantoates with respect to the DL-ammonium pantoate racemic mixture in various solvents is utilized for separating the two isomers. The thus-obtained D and L-ammonium pantoate are separated and are so treated that, following the addition of acid, the desired optically active pantolactone is isolated in conventional manner. DL-calcium pantoate is also susceptible to resolution by preferential crystallization in a manner similar to that used for separating racemic ammonium pantoate.

The foregoing methods have a number of disadvantages. The usefulness of the method for separating optical isomers by means of pairs of diastereoisomeric salts is limited by the bases that are required which are mostly naturally occurring alkaloids. Furthermore, because the cost of such bases is very high, it is necessary to recover the bases, which adds to the costs. Since these bases are also toxic or most highly active physiologically, this constitutes a further concomitant disadvantage. By racemization of the unwanted isomers the salt with the optically active base that is used must be cleaved into its separate components, otherwise the optically active base would also be racemized. This cleavage, combined with the further treatments that are required, represent a considerable additional expense.

By using L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol, which is an intermediate in the production of chloramphenicol, one is necessarily dependent upon the extent of the use of that compound in the production of chloramphenicol. The same reservations that apply to naturally occurring alkaloids also apply in the case of this resolving agent.

In the case of dehydroabietylamine the required higher dilution of the mixture that is to be resolved is a disadvantage because of the increased expenses that are incurred.

The use of diacyl-D-tartaric anhydrides is limited likewise by high cost and the treatments that are required as well as by the toxic solvents that are required.

Although a number of the disadvantages of processes of using optically active bases such as, for example, the difficulty of procuring the bases, their high cost, and the high cost for subsequently recovering the bases are avoided in the process of separating the optical isomers of pantolactone by preferential crystallization of ammonium pantoate because ammonia is readily available, the process is nonetheless fraught with a number of disadvantages. When pantolactone is reacted with ammonia, for example, the amide of pantoic acid is also obtained as well as the desired ammonium pantoate together with a series of further reaction products, such as amines and amides which to a great extent unfavorably affect the subsequent selective crystallization which is a very delicate procedure that is readily disturbed by even a small proportion of such by-products. Even with great care, the production of these by-products cannot be entirely avoided. A further disadvantage of the use of ammonium pantoate for separating the optical isomers of pantolactone from each other is that the unwanted isomer cannot readily be racemized. Ammonium pantoate cannot itself directly racemize since it is converted to various of the same by-products that form when pantolactone is reacted with ammonia. For the purpose of racemization, the unwanted ammonium pantoate

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must first be converted to pantolactone, which is then racemized and which then must be converted back to ammonium pantoate so that the optical isomers in the racemic mixture can then be separated from each other.

The use of selective crystallization for separating the isomers of DL-calcium pantoate as an amide of pantoic acid is also fraught with disadvantages. After separation of the optically active isomers, sodium methoxide in an nonaqueous medium must be used to racemize the unwanted isomeric component of the mixture. If only a fraction of 1% of water is present, the calcium pantoate is split into pantolactone and β-alanine and, if 1% water is present, the yield is only 50% of the theoretical, so that this reaction step can also involve high costs unless the splitting of the calcium pantothenate during the racemization can be completely prevented. Another disadvantage of this selective crystallization method is that it is limited to calcium pantoate, so that, when used for the preparation of D(+)-pantothenyl alcohol, optically active pantolactone is not formed and must be prepared in a separate operation.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a process for reducing substantially the cost of separating optical isomers of pantolactone, heretofore limited on one hand by the high cost of the resolving agents and on the other hand by the high cost of the processing treatments that were required.

Another object of the present invention is to provide a process for producing the optically active pantolactone in a high yield and in a high degree of purity.

The object of the present invention is accordingly to provide a process for resolving racemic pantolactone into its optical isomers without the use of optically active bases which are expensive and highly toxic resolving agents, by means of which the cost of resolving pantolactone in comparison with known processes is considerably reduced.

In accordance with the present invention, these objects are achieved by using a simple compound of racemic pantolactone, which on the one hand can be resolved either by selective crystallization or by electrostatic separation and on the other hand can be racemized and, after racemization and without further purification, the racemic mixture can be again resolved into its optical isomers.

It has been discovered that the foregoing objects can be achieved by using lithium pantoate, which can be prepared from basic lithium compounds and pantolactone in a polar solvent, preferably a lower alkanol or in water, or by metathesis of salts of pantoic acid, for example, calcium pantoate and lithium oxalate, or barium pantoate and lithium sulfate in an aqueous medium. Basic lithium compounds which can be used for the preparation of lithium pantoate are lithium carbonate and lithium hydroxide. Lithium pantoate in the presence of a polar solvent, preferably a lower alkanol, can be resolved into its optical isomers in accordance with conventional selective crystallization procedures, and the desired optically active form of lithium pantoate can then be converted in accordance with conventional methods into optically active pantolactone. A particular advantage of the process of the present invention is that it can be used to purify crude pantolactone by converting the pantolactone into the DL-lithium pantoate, which is thermally stable at the temperatures required and has a high coefficient of solubility with increasing temperature and which accordingly can be easily crystallized from saturated solutions thereof.

It was further discovered that the unwanted optically active form of lithium pantoate that is obtained as an accompanying by-product in the polar solvent, such as a lower alkanol, either dissolved or suspended therein, can be racemized to DL-lithium pantoate at a temperature between 120° and 180° C, in the presence of an alkaline catalyst, for example aliphatic amines, alkali-metal hydroxides or alkali-metal carbonates. The racemic lithium pantoate thus obtained can without further treatment or purification be subjected directly to resolution by selective crystallization.

The racemic mixture of lithium pantoate crystals obtained by crystallization from polar solvents can also be separated into its optical isomers in an electrostatic separator in accordance with conventional methods, as illustrated in Example 7 hereinafter.

The process of the present invention can be performed on a commercial scale with reduced expenditures for apparatus, for example, by eliminating the necessity for resolving, cleaving, and recovering the resolving agents after each separation before racemization, as well as expenditures for power. Further savings are realized by elimination of the requirement for purifying the pantolactone, and eliminating the costs of procuring the resolving agents, and losses resulting from their use, and further savings in operating time, which is made possible by the simplification achieved by the process of the present invention. By elimination of the requirement for the use of toxic substances, the working conditions and environment have also been improved.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

The processes of the present invention are further described and illustrated by the examples which follow.

EXAMPLE 1. Preparation of DL-lithium pantoate monohydrate.

A slurry of 1.00 kilogram of racemic DL-pantolactone and 300 grams of lithium carbonate in 1.5 liters of water was continuously stirred and heated at boiling temperature in a flask provided with a stirrer and reflux condenser for 1.5 hours. After all the evolved carbon dioxide had been expelled, the reaction mixture was filtered while hot and 25 grams of lithium carbonate was thus recovered therefrom. When the filtrate was cooled and stirred, 700 grams of crystals of racemic DL-lithium pantoate monohydrate having a melting point of 107°-110° C. amounting to 53.0% of the theoretical yield, separated and was collected. By evaporation of the mother liquor a further amount of DL-lithium pantoate, equivalent to 42% of the original DL-pantolactone, was recovered.

EXAMPLE 2. Preparation of anhydrous DL-lithium pantoate.

A slurry of 1.0 kilogram of DL-pantolactone (racemic) and 340 grams of lithium hydroxide monohydrate in 2.50 liters of methanol was heated at boiling temperature with continuous stirring for 2.5 hours in the apparatus that was described in Example 1. Carbon dioxide was thereafter injected into the reaction mixture and its hydrogen-ion concentration was brought to a value corresponding to a pH of 7.5. The lithium carbonate that was thus formed was then separated from the hot reaction mixture by filtration. After cooling, 620 grams of crystals of DL-lithium pantoate, having a melting point of 180°-182° C, were recovered from the filtrate, which amount is equivalent to 50% of the theoretical yield.

By evaporation of the mother liquor, DL-lithium pantoate monohydrate having a melting point of 107°-110° C, equivalent to 43% of the original pantolactone, was recovered.

EXAMPLE 3. Preparation of DL-lithium pantoate monohydrate.

A slurry of 334 grams of DL-calcium pantoate and 102 grams of lithium oxalate in 600 grams of water was heated at boiling temperature with continuous stirring in the apparatus described in Example 1 for 4 hours. The resulting mixture was then filtered while hot and the calcium oxalate that was thus separated was washed three times with 70-milliliter portions of hot water. The filtrate and wash waters were then combined and evaporated in a rotary vacuum evaporator to a volume of 400 milliliters during which 254 grams of DL-lithium pantoate monohydrate having a melting point of 107°-110° C, equivalent to 74% of the theoretical yield, separated and was collected. From the mother liquor by further concentration, DL-lithium pantoate monohydrate, in an amount equivalent to 20% of the original DL-pantolactone, was recovered.

EXAMPLE 4. Preparation of DL-lithium pantoate monohydrate.

A slurry of 431 grams of barium pantoate and 128 grams of lithium sulfate monohydrate in 1000 milliliters of water was heated at boiling temperature with continuous stirring for 6 hours in the apparatus described in Example 1 hereinbefore. Barium sulfate which formed in the reaction mixture was separated by filtration from the hot mixture and washed with three 80-milliliter portions of hot water. The filtrate and wash water were then combined and evaporated in a rotary vacuum evaporator as described in Example 3 and the DL-lithium pantoate recovered as therein described. A total of 320 grams of DL-lithium pantoate monohydrate having a melting point of 107°-110° C, equivalent to 93% of the theoretical yield, was thus obtained.

EXAMPLE 5. Separation of D-lithium pantoate from DL-lithium pantoate

To a solution of 50 grams of DL-lithium pantoate and 10 grams of D-lithium pantoate in 110 milliliters of methanol that was prepared by heating the mixture to a temperature of 60° C was added 0.1 gram of seed crystals of D-lithium pantoate. After stirring for 60 minutes and subsequently letting the seeded mixture stand for 3 hours, the crystals that formed in the solution were separated by filtration and dried. There was thus obtained 19 grams of D-lithium pantoate having an optical purity of 98% whose specific optical rotation $[\alpha]_D^{20}$ (c - 10.0) was 10.0°. (The symbol "c - 10.0" refers to a solution of 1 gram of the substance in 10 milliliters of water).

EXAMPLE 6. Separation of L-lithium pantoate from DL-lithium pantoate

A solution of 100 grams of DL-lithium pantoate and 8 grams of L-lithium pantoate in 1.1 liters of ethanol that was prepared by heating the mixture to a temperature of 62° C was inoculated with several seed crystals of L-lithium pantoate and cooled to a temperature of 2° C with continuous stirring and then permitted to stand undisturbed for 3 days at 2° C. The crystals thus formed in the solution were separated by filtration, washed successively with 10 milliters of ethanol and 5 milliliters of acetone and dried. In this manner was obtained 17 grams of L-lithium pantoate crystals having an optical purity of 87%, whose specific optical rotation $[\alpha]_D^{20}$ (c - 10.0) was 9.0°.

EXAMPLE 7. Resolution of DL-lithium pantoate into D(+)-lithium pantoate and L(−)-lithium pantoate

A solution of 895 grams of DL-lithium pantothenate in 1800 milliliters of methanol was prepared by stirring and warming the mixture to a temperature of 65° C. Subsequently this saturated solution was seeded with 1 gram of a mixture of crystals of pure D(+)-lithium pantoate and L(−)-lithium pantoate and the solution was cooled gradually to a temperature of 20° C at the rate of 0.33 centigrade degree per minute while it was stirred continuously. The crystals that thus formed in the solution were then separated by suction filtration and dried in the air, being continuously stirred during the drying period.

The dried crystalline material thus obtained, which consists of a racemic mixture of D-lithium pantoate and L-lithium pantoate was then subjected to separation in a free-fall separator comprising two metallic plate electrodes between which an electrostatic field having a electrical potential of 6 kilovolts per centimeter was maintained. In this manner, two fractions, each having an optical purity of 69%, were obtained.

To dissolve out the portions of racemic DL-lithium pantoate that each of these fractions contained, each fraction was stirred for 180 minutes with 1200 milliliters of methanol at a temperature of 25° C and subsequently cooled to a temperature of 10° C and stirred for an additional period of 60 minutes. The crystals were then separated from the methanol by suction filtration and dried. In this manner, 102 grams of pure D(+)-lithium pantoate and 108 grams of pure L(−)-lithium pantoate were obtained. The L(−)-lithium pantoate was subsequently subjected to racemization as described in Example 9 hereinafter.

The racemic DL-lithium pantoate that remained in solution in the methanol was crystallized therefrom by adding thereto a seed crystal of a racemic mixture of D-lithium pantoate and L-lithium pantoate.

EXAMPLE 8. Racemization of L(−)-lithium pantoate

To a solution of 57 grams of L(−)-lithium pantoate having a specific optical rotation $[\alpha]_D^{20}$ of −10.2° (c - 10.0) in 500 milliliters of methanol that was contained in a 1-liter autoclave was added 5 milliliters of diethylamine and the mixture was heated at a temperature of 160° C under its own autogenous pressure, which was a superatmospheric pressure of 17 atmospheres.

After cooling, the diethylamine was separated by distillation. Methanol was then added to the residue to form a suspension of DL-lithium pantoate crystals. In this manner 54 grams of DL-lithium pantoate, equivalent to 94.6% of the theoretical yield, was obtained by racemization of the L(−)-lithium pantoate. The D-lithium pantoate was separated from the DL-lithium pantoate thus obtained in accordance with the process described in Example 5 hereinbefore.

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EXAMPLE 9. Racemization of L(−)-lithium pantoate

To a solution of 100 grams of L(−)-lithium pantoate in 500 milliliters of methanol that was contained in a 1-liter autoclave was added 13.5 grams of lithium hydroxide monohydrate and the mixture was heated for 2.5 hours at a temperature of 160° C under its own autogenous pressure, which was a superatmospheric pressure of 17 atmospheres. The mixture was cooled and carbon dioxide was then passed into the mixture until the liquid portion of the mixture had a hydrogen-ion concentration corresponding to a pH of 7.5. The lithium carbonate that was thus formed was separated by filtration and the filtrate was evaporated to a concentration required for use in separation of the D-lithium pantoate from the resulting racemic mixture in accordance with the process described in Example 5 hereinbefore. The amount of DL-lithium pantoate that was thus obtained from the L(−)-lithium pantoate in this example was equivalent to 95% of the theoretical yield.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can by applying current knowledge readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspects of this invention.

What is claimed as new and described to be protected by Letters Patent is set forth in the appended claims.

1. Optically active D-lithium pantoate.

2. The process for obtaining the compound of claim 1 in separate form the said process comprising
   (a) forming a supersaturated solution of DL-lithium pantoate in a polar solvent;
   (b) subjecting the solution to crystallizing conditions while seeding it with crystals
      (a) of D-lithium pantoate so as to cause selective crystallization of the D-lithium pantoate from the solution, or
      (b) seeding the solution with both types of enantiomorphs of lithium pantoate followed by crystallization to obtain a racemic mixture of D-lithium pantoate and L-lithium pantoate and thereafter separating the mixture in in an electrostatic separator into two fractions of predominantly D(+) and L(−) lithium pantoate after dissolving out residual fractions of DL-lithium pantoate, and
   (c) finally recovering the D-lithium pantoate by separating it from the L-lithium pantoate.

3. The process of claim 2, wherein the obtained L-lithium pantoate is re-racemized and the thus formed D,L-lithium pantoate is recycled into the DL-lithium pantoate as starting compound.

4. The process of claim 3 wherein the re-racemization is effected by heating the L-lithium pantoate in form of a solution in a polar solvent to a temperature between 120° and 180° C in the presence of an alkaline catalyst.

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United States Patent [19]

Schmidt et al.

[11] **4,111,987**

[45] **Sep. 5, 1978**

[54] **LITHIUM PANTOATE AND OPTICALLY ACTIVE ISOMERS THEREOF AND PROCESS OF MAKING THE SAME**

[75] Inventors: **Joachim Schmidt; Christian Weigelt; Wolfgang Bamberg; Wolfgang** Schneider, all of Jena, Germany

[73] Assignee: **V E B Jenapharm**, Jena, Germany

[21] Appl. No.: **667,411**

[22] Filed: **Mar. 16, 1976**

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[63] Continuation of Ser. No. 407,254, Oct. 17, 1973, abandoned.

[51] **Int. Cl.**^{2} **C07C 59/04**
[52] **U.S. Cl.** **562/401**; 260/343.6
[58] **Field of Search** .... 260/535 R

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Primary Examiner—Paul J. Killos
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[57] ABSTRACT

A process for the resolution of optical isomers of racemic lithium pantoate by selective crystallization from a solution in methanol, ethanol, or other polar solvents, or by electrostatic separation. The optical isomers can be readily converted to optically active pantolactones which are the starting material for the preparation of optically active pantothenic acid and its salt and pantothenyl alcohol. One of the two optical isomers of each of these compounds possesses vitamin activity. The unwanted or inactive optical isomer of lithium pantoate as such is thermally stable and can be racemized by heating in the presence of a basic reacting compound at a temperature between 120° and 180° C to produce a racemic mixture which can then be subjected directly to resolution without conversion to some other derivative in accordance with the processes of the present invention to produce the desired or active optical isomer.

2 Claims, No Drawings

LITHIUM PANTOATE AND OPTICALLY ACTIVE ISOMERS THEREOF AND PROCESS OF MAKING THE SAME

This is a continuation of application Ser. No. 407,254, filed Oct. 17, 1973, now abandoned.

BACKGROUND OF THE INVENTION

The present invention pertains to processes for the resolution of optical isomers of lithium pantoate without the use of optically active resolving agents.

Pantolactone is used for the production of pantothenyl alcohol, pantothenic acid and its salts, such as, for example, calcium pantothenate, which possess vitamin activity and are useful as vitamins. Since such biological activity as vitamins is exhibited only by D(+) isomers, a method is required for resolving racemic mixtures of pantolactone. The resolution can be effected either with pantolactone itself or with calcium pantothenate.

Of the many conventional methods for the resolution of optical isomers, such as adsorption, distillation, use of resolving agents, enzymatic or microbiological separation, conversion to diastereoisomeric pairs of salts, selective or preferential crystallization, and electrostatic separation, the only methods that have been found heretofore to be suitable for the resolution of optical isomers of pantolactone were the use of diastereoisomeric pairs of salts or preferential crystallization of ammonium pantoate which latter method is described, for example, in U.S. Pat. No. 3,529,022. Optical isomers of calcium pantothenate can also be resolved by preferential crystallization.

For separation by formation of pairs of diastereoisomeric salts, the process consists generally either in conversion of the racemic mixture of pantolactones with a suitable optically active base, or conversion of a metal salt of the racemic mixture of pantolactone with a salt of an optically active base and a strong acid. This conversion is effected generally in an alcoholic, aqueous alcoholic, or aqueous medium. There is thus obtained a salt of an optically active isomer having a degree of purity that is dependent upon the solvent and the base used. The corresponding enantiomorphs remain in the mother liquor. The salt and the mother liquor are then separated and the salt is treated in such manner that, after addition of acid, the desired optical isomer of pantolactone is isolated and the base is recovered. The unwanted optically inactive isomer of pantolactone is racemized and the racemic mixture is again resolved to obtain the desired optical isomer.

Optically active bases that were used heretofore included naturally occurring alkaloids such as quinine and ephedrine as well as synthetic optically active compounds such as L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol. Of the synthetic optically active compounds, β-phenylethylamine and dehydroabietylamine are also of importance.

Another method of resolving DL-pantolactones which is described in U.S. Pat. No. 2,383,524 depends upon the use of anhydrides of diacyl-D-tartaric acids, with which the pantolactone is esterified. Pyridine salts of the racemic esters are then formed and, because of their differences in solubility in benzene, the optical isomers are then separated from each other.

For separating racemic pantolactone into its optical isomers by means of preferential crystallization, the racemic mixture is converted into the corresponding ammonium salt and the differences in solubilities of the D and L-ammonium pantoates with respect to the DL-ammonium pantoate racemic mixture in various solvents is utilized for separating the two isomers. The thus-obtained D and L-ammonium pantoate are separated and are so treated that, following the addition of acid, the desired optically active pantolactone is isolated in conventional manner. DL-calcium pantothenate is also susceptible to resolution by preferential crystallization in a manner similar to that used for separating racemic ammonium pantoate.

The foregoing methods have a number of disadvantages. The usefulness of the method for separating optical isomers by means of pairs of diastereoisomeric salts is limited by the bases that are required which are mostly naturally occurring alkaloids. Furthermore, because the cost of such bases is very high, it is necessary to recover the bases, which adds to the costs. Since these bases are also toxic or most highly active physiologically, this constitutes a further concomitant disadvantage. By racemization of the unwanted isomers the salt with the optically active base that is used must be cleaved into its separate components, otherwise the optically active base would also be racemized. This cleavage, combined with the further treatments that are required, represent a considerable additional expense.

By using L-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol, which is an intermediate in the production of chloramphenicol, one is necessarily dependent upon the extent of the use of that compound in the production of chloramphenicol. The same reservations that apply to naturally occurring alkaloids also apply in the case of this resolving agent.

In the case of dehydroabietylamine the required higher dilution of the mixture that is to be resolved is a disadvantage because of the increased expenses that are incurred.

The use of diacyl-D-tartaric acid anhydrides is limited likewise by high cost and the treatments that are required as well as by the toxic solvents that are required.

Although a number of the disadvantages of processes of using optically active bases such as, for example, the difficulty of procuring the bases, their high cost, and the high cost for subsequently recovering the bases are avoided in the process of separating the optical isomers of pantolactone by preferential crystallization of ammonium pantoate because ammonia is readily available, the process is nonetheless fraught with a number of disadvantages. When pantolactone is reacted with ammonia, for example, the amide of pantoic acid is also obtained as well as the desired ammonium pantoate together with a series of further reaction products, such as amines and amides which to a great extent unfavorably affect the subsequent selective crystallization which is a very delicate procedure that is readily disturbed by even a small proportions of such by-products. Even with great care, the production of these by-products cannot be entirely avoided. A further disadvantage of the use of ammonium pantoate for separating the optical isomers of pantolactone from each other is that the unwanted isomer cannot readily be racemized. Ammonium pantoate cannot itself directly racemize since it is converted to various of the same by-products that form when pantolactone is reacted with ammonia. For the purpose of racemization, the unwanted ammonium pantoate must first be converted to pantolactone, which is then racemized and which then must be converted back to

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ammonium pantoate so that the optical isomers in the racemic mixture can then be separated from each other.

The use of selective crystallization for separating the isomers of DL-calcium panothenate as an amide of pantoic acid is also fraught with disadvantages. After separation of the optically active isomers, sodium methoxide in an nonaqueous medium must be used to racemize the unwanted isomeric component of the mixture. If only a fraction of 1% of water is present, the calcium pantothenate is split into pantolactone and β-alanine and, if 1% water is present, the yield is only 50% of the theoretical, so that this reaction step can also involve high costs unless the splitting of the calcium pantothenate during the racemization can be completely prevented. Another disadvantage of this selective crystallization method is that it is limited to calcium pantothenate, so that, when used for the preparation of D(+)-pantothenyl alcohol, optically active pantolactone is not formed and must be prepared in a separate operation.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a process for reducing substantially the cost of separating optical isomers of pantolactone, heretofore limited on one hand by the high cost of the resolving agents and on the other hand by the high cost of the processing treatments that were required.

Another object of the present invention is to provide a process for producing the optically active pantolactone in a high yield and in a high degree of purity.

The object of the present invention is accordingly to provide a process for resolving racemic pantolactone into its optical isomers without the use of optically active bases which are expensive and highly toxic resolving agents, by means of which the cost of resolving pantolactone is comparison with known processes is considerably reduced.

In accordance with the present invention, these objects are achieved by using a simple compound of racemic pantolactone, which on the one hand can be resolved either by selective crystallization or by electrostatic separation and on the other hand can be racemized and, after racemization and without further purification, the racemic mixture can be again resolved into its optical isomers.

It has been discovered that the foregoing objects can be achieved by using lithium pantoate, which can be prepared from basic lithium compounds and pantolactone in a polar solvent, preferably a lower alkanol or in water, or by metathesis of salts of pantoic acid, for example, calcium pantoate and lithium oxalate, or barium pantoate and lithium sulfate in an aqueous medium. Basic lithium compounds which can be used for the preparation of lithium pantoate are lithium carbonate and lithium hydroxide. Lithium pantoate in the presence of a polar solvent, preferably a lower alkanol, can be resolved into its optical isomers in accordance with conventional selective crystallization procedures, and the desired optically active form of lithium pantoate can then be converted in accordance with conventional methods into optically active pantolactone. A particular advantage of the process of the present invention is that it can be used to purify crude pantolacfone by converting the pantolactone into the DL-lithium pantoate, which is thermally stable at the temperatures required and has a high coefficient of solubility with increasing temperature and which accordingly can be easily crystallized from saturated solutions thereof.

It was further discovered that the unwanted optically active form of lithium pantoate that is obtained as an accompanying by-product in the polar solvent, such as a lower alkanol, either dissolved or suspended therein, can be racemized to DL-lithium pantoate at a temperature between 120° and 180° C, in the presence of an alkaline catalyst, for example aliphatic amines, alkali-metal hydroxides or alkali-metal carbonates. The racemic lithium pantoate thus obtained can without further treatment or purification be subjected directly to resolution by selective crystallization.

The racemic mixture of lithium pantoate crystals obtained by crystallization from polar solvents can also be separated into its optical isomers in an electrostatic separator in accordance with conventional methods, as illustrated in Example 7 hereinafter.

The process of the present invention can be performed on a commercial scale with reduced expenditures for apparatus, for example, by eliminating the necessity for resolving, cleaving, and recovering the resolving agents after each separation before racemization, as well as expenditures for power. Further savings are realized by elimination of the requirement for purifying the pantolactone, and eliminating the costs of procuring the resolving agents, and losses resulting from their use, and further savings in operating time, which is made possible by the simplification achieved by the process of the present invention. By elimination of the requirement for the use of toxic substances, the working conditions and environment have also been improved.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

The processes of the present invention are further described and illustrated by the examples which follow.

EXAMPLE 1

Preparation of DL-lithium pantoate monohydrate.

A slurry of 1.00 kilogram of racemic DL-pantolactone and 300 grams of lithium carbonate in 1.5 liters of water was continuously stirred and heated at boiling temperature in a flask provided with a stirrer and reflux condenser for 1.5 hours. After all the evolved carbon dioxide had been expelled, the reaction mixture was filtered while hot and 25 grams of lithium carbonate was thus recovered therefrom. When the filtrate was cooled and stirred, 700 grams of crystals of racemic DL-lithium pantoate monohydrate having a melting point of 107°-110° C, amounting to 53.0% of the theoretical yield, separated and was collected. By evaporation of the mother liquor a further amount of DL-lithium pantoate, equivalent to 42% of the original DL-pantolactone, was recovered.

EXAMPLE 2

Preparation of anhydrous DL-lithium pantoate.

A slurry of 1.0 kilogram of DL-pantolactone (racemic) and 340 grams of lithium hydroxide monohydrate in 2.50 liters of methanol was heated at boiling temperature with continuous stirring for 2.5 hours in the apparatus that was described in Example 1. Carbon dioxide was thereafter injected into the reaction mixture and its hydrogenion concentration was brought to a value corresponding to a pH of 7.5. The lithium carbonate that was thus formed was then separated from the hot reaction mixture by filtration. After cooling, 620 grams of crystals of DL-lithium pantoate, having a melting point of 180°-182° C, were recovered from the filtrate, which amount is equivalent to 50% of the theoretical yield.

By evaporation of the mother liquor, DL-lithium pantoate monohydrate having a melting point of 107°-110° C, equivalent to 43% of the original pantolactone, was recovered.

EXAMPLE 3

Preparation of DL-lithium pantoate monohydrate.

A slurry of 334 grams of DL-calcium pantoate and 102 grams of lithium oxalate in 600 grams of water was heated at boiling temperature with continuous stirring in the apparatus described in Example 1 for 4 hours. The resulting mixture was then filtered while hot and the calcium oxalate that was thus separated was washed three times with 70-milliliter portions of hot water. The filtrate and wash waters were then combined and evaporated in a rotary vacuum evaporator to a volume of 400 milliliters during which 254 grams of DL-lithium pantoate monohydrate having a melting point of 107°-110° C, equivalent to 74% of the theoretical yield, separated and was collected. From the mother liquor by further concentration, DL-lithium pantoate monohydrate, in an amount equivalent to 20% of the original DL-pantolactone, was recovered.

EXAMPLE 4

Preparation of DL-lithium pantoate monohydrate.

A slurry of 431 grams of barium pantoate and 128 grams of lithium sulfate monohydrate in 1000 milliliters of water was heated at boiling temperature with continuous stirring for 6 hours in the apparatus described in Example 1 hereinbefore. Barium sulfate which formed in the reaction mixture was separated by filtration from the hot mixture and washed with three 80 milliliter portions of hot water. The filtrate and wash water were then combined and evaporated in a rotary vacuum evaporator as described in Example 3 and the DL-lithium pantoate recovered as therein described. A total of 320 grams of DL-lithium pantoate monohydrate having a melting point of 107°-110° C, equivalent to 93% of the theoretical yield, was thus obtained.

EXAMPLE 5

Separation of D-lithium pantoate from DL-lithium pantoate.

To a solution of 50 grams of DL-lithium pantoate and 10 grams of D-lithium pantoate in 110 milliliters of methanol that was prepared by heating the mixture to a temperature of 60° C was added 0.1 gram of seed crystals of D-lithium pantoate. After stirring for 60 minutes and subsequently letting the seeded mixture stand for 3 hours, the crystals that formed in the solution were separated by filtration and dried. There was thus obtained 19 grams of D-lithium pantoate having an optical purity of 98% whose specific optical rotation $[\alpha]D^{20}$ (*c* = 10.0) was 10.0°. (The symbol "*c* = 10.0" refers to a solution of 1 gram of the substance in 10 milliliters of water).

EXAMPLE 6

Separation of L-lithium pantoate from DL-lithium pantoate.

A solution of 100 grams of DL-lithium pantoate and 8 grams of L-lithium pantoate in 1.1 liters of ethanol that was prepared by heating the mixture to a temperature of 62° C was inoculated with several seed crystals of L-lithium pantoate and cooled to a temperature of 2° C with continuous stirring and then permitted to stand undisturbed for 3 days at 2° C. The crystals thus formed in the solution were separated by filtration, washed successively with 10 milliliters of ethanol and 5 milliliters of acetone and dried. In this manner was obtained 17 grams of L-lithium pantoate crystals having an optical purity of 87%, whose specific optical rotation $[\alpha]D^{20}$ (c = 10.0 was 9.0°.

EXAMPLE 7

Resolution of DL-lithium pantoate into D(+)-lithium pantoate and L(−)-lithium pantoate.

A solution of 895 grams of DL-lithium pantothenate in 1800 milliliters of methanol was prepared by stirring and warming the mixture to a temperature of 65° C. Subsequently this saturated solution was seeded with 1 gram of a mixture of crystals of pure D(+)-lithium pantoate and L(−)-lithium pantoate and the solution was cooled gradually to a temperature of 20° C at the rate of 0.33 centigrade degree per minute while it was stirred continuously. The crystals that thus formed in the solution were then separated by suction filtration and dried in the air, being continuously stirred during the drying period.

The dried crystalline material thus obtained, which consists of a racemic mixture of D-lithium pantoate and L-lithium pantoate was then subjected to separation in a free-fall separator comprising two metallic plate electrodes between which an electrostatic field having an electrical potential of 6 kilovolts per centimeter was maintained. In this manner, two fractions, each having an optical purity of 69%, were obtained.

To dissolve out the portions of racemic DL-lithium pantoate that each of these fractions contained, each fraction was stirred for 180 minutes with 1200 milliliters of methanol at a temperature of 25° C and subsequently cooled to a temperature of 10° C and stirred for an additional period of 60 minutes. The crystals were then separated from the methanol by suction filtration and dried. In this manner, 102 grams of pure D(+)-lithium pantoate and 108 grams of pure L(−)-lithium pantoate were obtained. The L(−)-lithium pantoate was subsequently subjected to racemization as described in Example 9 hereinafter.

The racemic DL-lithium pantoate that remained in solution in the methanol was crystallized therefrom by adding thereto a seed crystal of a racemic mixture of D-lithium pantoate and L-lithium pantoate.

EXAMPLE 8

Racemization of L(−)-lithium pantoate

To a solution of 57 grams of L(−)-lithium pantoate having a specific optical rotation $[\alpha]D^{20}$ of −10.2° (c = 10.0) in 500 milliliters of methanol that was contained in a 1-liter autoclave was added 5 milliliters of diethylamine and the mixture was heated at a temperature of 160° C under its own autogenous pressure, which was a superatmospheric pressure of 17 atmospheres.

After cooling, the diethylamine was separated by distillation. Methanol was then added to the residue to form a suspension of DL-lithium pantoate crystals. In this manner 54 grams of DL-lithium pantoate, equivalent to 94.6% of the theoretical yield, was obtained by racemization of the L(−)-lithium pantoate. The D-lithium pantoate was separated from the DL-lithium pantoate thus obtained in accordance with the process described in Example 5 hereinbefore.

EXAMPLE 9

Racemization of L(−)-lithium pantoate

To a solution of 100 grams of L(−)-lithium pantoate in 500 milliliters of methanol that was contained in a 1-liter autoclave was added 13.5 grams of lithium hydroxide monohydrate and the mixture was heated for 2.5 hours at a temperature of 160° C under its own autogenous pressure, which was a superatmospheric pressure of 17 atmospheres. The mixture was cooled and carbon dioxide was then passed into the mixture until the liquid portion of the mixture had a hydrogen-ion concentration corresponding to a pH of 7.5. The lithium carbonate that was thus formed was separated by filtration and the filtrate was evaporated to a concentration required for use in separation of the D-lithium pantoate from the resulting racemic mixture in accordance with the process described in Example 5 hereinbefore. The amount of DL-lithium pantoate that was thus obtained from the L(−)-lithium pantoate in this example was equivalent to 95% of the theoretical yield.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can by applying current knowledge readily adapt it for various applications without omitting features that, from the standpoint of prior art, fairly constitute essential characteristics of the generic or specific aspects of this invention.

What is claimed as new and described to be protected by Letters Patent is set forth in the appended claims:

1. The process of making DL-lithium pantoate comprising reacting D,L-calcium pantoate and lithium oxalate in a solvent for the reactants and in amounts of the two salts to permit effecting a metathesis of the two salts, the reaction being carried out at the boiling point of the solvent, then separating the calcium oxalate from the DL-lithium pantoate and recovering the latter compound in the form of its monohydrate.

2. The process of making DL-lithium pantoate comprising reacting DL-barium pantoate and lithium sulfate in a solvent at its boiling point and in amounts of the two salts to permit effecting a metathesis of the two salts followed by separating the barium sulfate from the DL-lithium pantoate and recovering the latter compound in the form of its monohydrate.

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PROCESS FOR OPTICAL RESOLUTION OF CALCIUM PANTOTHENATE

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ABSTRACT OF THE DISCLOSURE

An optical resolution of a mixture of D- and L-calcium pantothenates from a supersaturated aqueous methanol solution thereof alternately seeding the solution with one kind of crystals of the two enantiomers to separate the seeded enantiomer, said crystals having one molecular of water of crystallization and four molecules of methanol of crystallization, thus selectively and alternately crystallizing and separating the two enantiomers.

This invention relates to a process for optical resolution of racemic calcium pantothenate.

D-pantothenic acid is a chemical substance which plays an important role in a biochemical reaction in vivo as a constituent of coenzyme A, and its calcium salt has been employed as a valuable medicine. Calcine pantothenate can be produced today by chemical synthesis. The product synthesized by usual methods is, however, inevitably obtained in a racemic form and, in order to obtain optically pure D-calceuim pantothenate, an optical resolution must be carried out in an intermediate or final stage of the synthesis.

The processes hitherto known to the art for the optical resolution are in general classified in two groups. One method involves the optical resolution of α-hydroxy-β,β-dimethyl-γ-butyrolactone, also referred to as pantolactone, an intermediate product of pantothenic acid, using as a resolving agent a natural alkaloid such as quinine, brucine or an amine such as phenylethylamine or galactamine (for instance U.S. Patent No. 2,319,545, U.S. Patent No. 2,390,281, German Patent No. 16,482, and British Patent No. 773,174). The other is a process which involves optically resolving the final product, i.e. pantothenic acid, using as a resolving agent a natural alkaloid such as quinine or cinchonidine, or its derivatives (R. Kuhn et al., Chem. Ber. 73, 971 and 1134 (1940); U.S. Patent No. 2,341,610; E. T. Stiller et al., J. Am. Chem. Soc. 63, 1237 (1941); and British Patent No. 554, 558).

These processes, however, cannot be deemed to be industrially advantageous because the use of said resolving agents complicates the manufacturing procedures and demands huge investments for the equipment and, moreover, the loss of the expensive resolving agents in the course of recovery and refining operations can be a materially adverse cost factor.

Accordingly, an object of the invention is to improve the optical resolution of racemic calcium pantothenate.

Another object is to provide a method for resolving racemic calcium pantothenate economically by a simple procedure.

Another object is to provide a method for resolving racemic calcium pantothenate by selective alternate crystallization of the enantiomers thereof.

A further object is to obtain D-calcium pantothenate of optically high purity in larger yields when compared with prior art procedures.

The other objects and advantages will be apparent from the following detailed description and claims.

As a result of extensive studies on the subject, it has been found that the solubility of optically active calcium pantothenate in hydrous methanol is considerably less than that of the salt of optically inactive racemate and, on the basis of the result, the process of the present invention has been completed, whereby racemic calcium pantothenate is optically resolved through a direct crystallization procedure i.e. a seeding method without the use of any resolving agent.

More particularly, the present invention is a process for the optical resolution of racemic calcium pantothenate which comprises seeding a supersaturated aqueous methanol solution of racemic calcium pantothenate with seed crystals of either D-calcium pantothenate or L-calcium pantothenate, thereby selectively and alternately crystallizing either D-calcium pantothenate or L-calcium pantothenate.

The present invention will be more fully described hereinafter.

While the soluble amounts of optically active D-calcium pantothenate and L-calcium pantothenate in 100 ml. of 98% methanol at 5° C. are, respectively, 0.23 g. and 0.25 g., that of the racemate is 55.8 g. Thus, in a aqueous methanol solution containing the antipode, the optically active salt will dissolve to a degree beyond its own solubility and will not crystallize when allowed to stand for a long time, maintaining a stable supersaturated state.

In the process of the invention, the seed crystals to be employed are optically active D-calcium pantothenate and L-calcium pantothenate crystallized from an aqueous methanol solution. On drying at a low temperature they attain a constant weight with calcium pantothenate purity 76.5% and show a loss of 23.5% on drying with heat. They melt at 55° C. and are resolidified at 70°–80° C. They have decomposition points of 195°–196° C. and $[\alpha]_D^{25} \pm (21.0\text{–}21.3°)$ (c.=5, H_2O). The crystals apparently contain crystal solvents, and the composition has been clarified by use to have one molecule of water of crystallization and four molecules of methanol of crystallization.

When an optically active salt having one molecule of water of crystallization and four molecules of methanol of crystallization is added as seed crystals to a supersaturated aqueous methanol solution of the above-mentioned racemate at a temperature below an ordinary temperature, then the seed crystals on stirring will not be dissolved in the solution but will be thoroughly dispersed, permitting deposition of crystals of the same optically active salt as the seeded one.

In contrast therewith, when the crystals of an optically active salt dried in the usual manner or recrystallized from different kinds of solvents are used as the seed crystals, they will be easily dissolved in the solution and fail to serve as such if the amount is too small. On the contrary, if the amount is too large, they will be conglomerated and will not disperse well. In the latter case, recrystallization takes place around partially undissolved crystals, and the resulting crystals containing the solvents of crystallization serve as crystal nuclei for further crystal growth. However, the rate of crystallization is low and the crystals thus separated are inferior in optical purity.

For the purpose of industrially obtaining crystals having very high optical purity in a high yield, it is necessary to use as the seed crystals those referred to above which have one molecule of water of crystallization and four molecules of methanol of crystallization. The ~~seed~~ crystals used in the present invention are usually those which are finely pulverised and may have a free solvent thereon, from which the crystals have been separated.

In practising the process of the invention, it is theoretically necessary that the water content of the solution is at least equimolecular to the dissolved racemic calcium pantothenate. Actually, however, the desirable racemic calcium pantothenate concentration in the solution is 20–35% w./v. and the desirable water content is in the range of 2–15, preferably 2–7% w./v. Any water content outside the above range will deprive the present invention of its economical feature.

Although an increase in the concentration of racemic calcium pantothenate will usually bring about a favorable effect, the concentration in excess of 35% w./v. will rather increase the viscosity to such an extent that difficulties will be involved in the filtration and other treatment of the solution. Furthermore, a crystallization operation with such a high concentration of racemic calcium pantothenate tends to deposit the salt of undesired antipode, thus rendering it difficult to obtain an optically active salt with high purity.

For the reasons above explained, the concentration of racemic calcium pantothenate in a solution is preferably in the range of 20–35% w./v., and most preferably of 30–33% w./v. for the purpose of an industrial process. The optically active salt to be added as seed crystals is fully effective even in an amount of about 0.5% in weight of the amount of racemic calcium pantothenate dissolved.

The crystallization temperature may be at or below an ordinary temperature, but a too low temperature is not desirable for the operation because the crystals so formed are too fine, though the crystallization rate is increased. Moreover, the optical purity of the resolved crystals is adversely affected. The crystallization temperature is, therefore, preferably in the range of 5°–15° C.

In order to carry out the optical resolution favorably by crystallization procedure, constant stirring at such a rather low speed that the separated crystals will be kept from being deposited on the bottom of the reaction vessel is required. If the solution is vigorously stirred, the excessive stimulation will partly destroy the supersaturated state of the optically active salt, lowering the optical purity of the crystals so separated. Conversely, if the stirring speed is too low, the crystals will deposit on the bottom of the reaction vessel and again give the same adverse effects.

When, under the conditions as described above, an optical active salt having one molecule of water of crystallization and four molecules of methanol of crystallization is added as seed crystals to a supersaturated aqueous methanol solution of racemic calcium pantothenate and crystals of the same optically active salt as the seeded crystals are separated, whereby optical resolution is accomplished in a favorable way.

Observing the separation of crystals or the progress of resolution in terms of the angle of rotation of the solution, the angle of rotation shows a linear change with the lapse of time and, when the supersaturated state of the salt of unseeded enantiomer begins to be broken after a certain period of time, the absolute value of the angle reaches a maximum and then trends downward.

It thus follows that, if the crystallizing operation is discontinued at the point where the salt of unseeded enantiomer is about to begin crystallizing and the crystals so formed are separated, an optically active salt of a high purity can be obtained in a maximum yield. If the crystallizing operation is controlled as above through continuous observation of the change of the rotation angle of the solution, it is possible to obtain an optically active salt of a very high purity with an absolute value of the specific rotation of more than 25°.

The crystals are recovered in a simple manner by filtration, centrifugation, or the like, and are then washed and dried if desired.

The removal of the seeded salt leaves the solution supersaturated with the unseeded salt which makes of course the solution optically active, the solution exhibiting contrary rotation to that of the separated crystals. Therefore, the salt of unseeded enantiomer having the same solvents of crystallization in the same proportion as those of the salt of seeded enantiomer can be added to the filtrate in the same as described above, thereby to crystallize the salt of the enantiomer left in the filtrate similarly in a high purity.

In order to carry out this process for optical resolution advantageously on an industrial basis, it is advisable to replenish mother liquor from which one of the salts of the enantiomers has been separated with the racemic salt in an amount corresponding to the separated salt of the enantiomer, thus selectively and alternately crystallizing the salts of the both enantiomers. When the optical resolution is accomplished by the alternate crystallization procedures as described above, optically active salts of a high purity can be obtained in a yield of 25–40% of the amount of dissolved racemic calcium pantothenate out of a solution containing racemic calcium pantothenate at a concentration of 30–33% w./v.

As described hereinbefore, the process of the invention permits to obtain optically active salt in a high yield through extremely simplified operations, providing a most beneficial industrial process with economic advantages as compared wtih the prior art techniques for chemical resolution which use expensive resolving agents.

The invention can be further illustrated by the following example which is not intended to limit the present invention:

EXAMPLE

When wet D-calcium pantothenate or L-calcium pantothenate recrystallized from aqueous methanol was dried under reduced pressure in a calcium chloride disiccator, it attained a constant weight in three to four hours. The material so dried has a melting point of 55° C. and $[\alpha]_D^{25}\pm(21.0°-21.3°)$ (c.=5, H_2O), and the content of calcium pantothenate amounts to about 76.5%. It was pulverized to form fine crystals, 200 mesh or less in size, as seed crystals.

400 g. of rac.-calcium pantothenate was added to about 1400 ml. of about 98% methanol, dissolved by heating at about 40° C., and filtered. To the filtrate, methanol was added to make up to a total liquid amount of 1700 ml. The concentration of calcium pantothenate in this solution was 23.5% w./v. and the water content was 2.9% w./v. To the solution, while stirring slowly at 9°–10° C., 3 g. of seed crystals of L-calcium pantothenate was added. With the lapse of time, the amount of separated crystals increased. After one hour and forty minutes since the addition of the seed crystals, the stirring was stopped and separated crystals were recovered by filtration. The crystals on drying gave 76 g. of L-calcium pantothenate, $[\alpha]_D^{25}-25.3°$ (c.=5, H_2O).

The filtrate, after removal of L-calcium pantothenate, had an angle of rotation of +0.93° (as determined at 20°–25° C., with wave length of 589 mμ and layer length of 5 cm. The same is applied hereinafter). To the filtrate, 200 g. of rac.-calcium pantothenate was added and dissolved at 40°–45° C., The solution was filtered and the filtrate was replenished with aqueous methanol to make up to 1700 ml., or the same amount as the original solution. The concentration of calcium pantothenate in the solution was 30.6% w./v., the water content was 3.0% w./v., and the angle of rotation was +0.73°. With slow stirring at 13°–14° C., 3 g. of seed crystals of D-calcium pantothenate was added to the solution. When allowed to crystallize over a period of three hours and ten minutes, the angle of rotation of the mother liquor dropped to −0.99°. Immediately it was filtered, and the separated crystals were washed with 240 ml. of methanol and dried. There was obtained 177 g. of D-calcium pantothenate having $[\alpha]_D^{25}+26.0°$ (c.=5, H_2O).

The filtrate from which D-calcium pantothenate had been separated was now replenished in the same way as described above with 200 g. of rac.-calcium pantothenate

XIV

and the resulting solution was filtered. To the filtrate, methanol was added to make up to 1700 ml. The solution had a calcium concentration of 31.2% w./v., water content of 3.2% w./v., and angle of rotation of 0.76°. While the solution was kept at 9°–10° C. and stirred slowly, 3 g. of seed crystals of L-calcium pantothenate was added. After crystallization for over a period of 3 hours, the solution showed an angle of rotation of +0.97°. It was immediately filtered and the crystals were washed with 240 ml. of methanol and dried. There was obtained 172 g. of L-calcium pantothenate having $[\alpha]_D^{25}-25.0^\circ$ (c.=5, H_2O).

The filtrate from which L-calcium pantothenate was separated was supplied with 190 g. of rac.-calcium pantothenate in the same manner as described above. The resulting solution was filtered and the filtrate was made up to a total amount of 1700 ml. with the addition of methanol. The solution had a concentration of calcium pantothenate of 31.5% w./v., water content of 3.0% w./v., an angle of rotation of +0.75°. While the solution was being stirred slowly at 9°–10° C., there was added 3 g. of seed crystals of D-calcium pantothenate. After crystallization for over a period of three hours, the angle of rotation of the solution dropped to −0.98°. It was filtered, and the crystals on washing with 240 ml. of methanol and drying gave 175 g. of D-calcium pantothenate having $[\alpha]_D^{25}+25.6^\circ$ (c.=5, H_2O). The same procedures were thereafter repeated, whereby D-calcium pantothenate and L-calcium pantothenate could be alternately obtained.

What is claimed is:

1. A process for the optical resolution of racemic calcium pantothenate which comprises seeding a supersaturated aqueous methanolic solution of racemic calcium pantothenate with crystals of the desired optically active isomer, said aqueous methanolic solution containing water in an amount of 2 to 15% w./v. and said crystals containing one molecule of water of crystallization and four molecules of methanol of crystallization, and effecting resolution at a temperature between 5° and 15° C. to obtain crystals of the same optically active isomer as the seed crystals.

2. A process according to claim 1 wherein the seeded solution is gently stirred at a speed to prevent the separated crystals from being deposited on the bottom of the reaction vessel.

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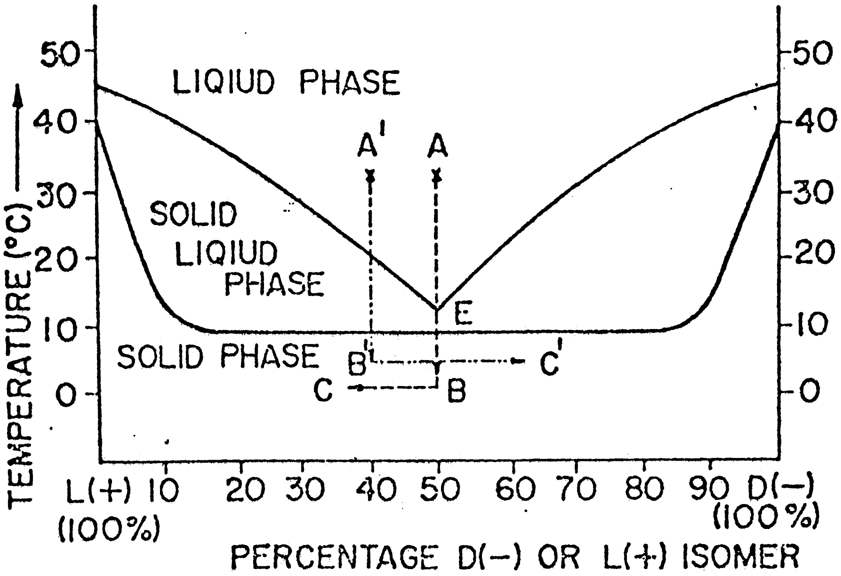
LORRAINE A. WEINBERGER, Primary Examiner

A. P. HALLUIN, Assistant Examiner

May 8, 1973 SABURO NABETA ET AL 3,732,255

PROCESS FOR OPTICAL RESOLUTION OF O-ACETYLPANTOLACTONE

Filed Sept. 30, 1969



United States Patent Office

3,732,255

Patented May 8, 1973

3,732,255

PROCESS FOR OPTICAL RESOLUTION OF O-ACETYLPANTOLACTONE

Saburo Nakata, Ieji Kuniyoshi, and Masahiro Inagaki, Chiba, Japan, assignors to Daiichi Seiyaku Company, Limited, Tokyo, Japan

Filed Sept. 30, 1969, Ser. No. 862,436
Claims priority, application Japan, Sept. 30, 1968, 43/70,105
Int. Cl. C07d *5/06*
U.S. Cl. 260—343.6 6 Claims

ABSTRACT OF THE DISCLOSURE

Optically resolving a mixture of D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone by seeding a homogeneous liquid mixture of these two materials with optically active seed crystals of either of the two enantiomers in a binary system. The same isomer as the seed crystals is crystallized and the precipitate can be recovered.

BACKGROUND OF THE INVENTION

Field of the invention

The present invention relates to a novel process for the optical resolution of O-acetylpantolactone in a binary system.

D(−)-pantolactone is an intermediate useful in medicines, such as calcium D(+)-pantothenate, D(+)-pantothenyl alcohol, D(+)-panthetin and so on. It has generally been prepared by the optical resolution of racemic pantolactone.

Description of the prior art

In processes for obtaining optically active pantolactone from racemic pantolactone, the following agents have been used for the resolution thereof:

Quinine (U.S. Pat. No. 2,319,545), brucine (U.S. Pat. No. 2,390,281) or strychnine (Chemical Abstracts 41, 6199 (1947)); galactamine (British Pat. No. 773,174), l-α-phenylethylamine (Pharmazie 12, 254 (1957) German Pat. No. 16,482 and U.S. Pat. No. 3,185,710) and L-amino acids (Japanese patent publication No. 12149/68).

Further, it is known that racemic pantolactone reacts with aqueous ammonia to give ammonium pantoate, which can be resolved by selective crystallization from aqueous alcohols into optically active isomers of ammonium pantoate (Belgian Pat. No. 698,139). However, these known methods have various disadvantageous and unsatisfactory features from an industrial viewpoint.

For instance, in the case of using a resolving agent, resolving agents are so expensive that complicated procedures and operations are required in order to get the best recovery of the resolving agent. Further, the yields are not always good. For instance, in producing racemic ammonium pantoate, it has been found that the formation of racemic pantoamide is inevitable (as a byproduct) in the reaction of racemic pantolactone with an aqueous ammonium solution. Accordingly, it is necessary to purify racemic ammonium pantoate. Further, the stability of a supersaturated solution of racemic ammonium pantoate is not satisfactory enough for selective crystallization, and consequently contamination of racemic pantolactone in the optically active isomer is inevitable.

As stated above, the hitherto known methods are not advantageous for an industrial use.

As the result of studies on the optical resolution of pantolactone, the inventors have succeeded in establishing a very advantageous method for the production of optically active pantolactone obtained via the resolution of DL-O-acetylpantolactone.

SUMMARY OF THE INVENTION

The present invention provides a novel method for the optical resolution of a mixture of D-acetylpantolactone and L(+)-O-acetylpantolactone which comprises seeding a homogeneous phase composed of D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone with optically active seed crystals of either of the two optical isomers in a binary system. The terminology "binary system" indicates a homogeneous liquid phase composed of the two optically active isomers, D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone. Optical resolution is at a low temperature, preferably below 13.5° C., and the same isomer as the seed crystal is crystallized from the mixture. The precipitate can be recovered to yield the final product.

An object of this invention is to provide an advantageous method for the optical resolution of O-acetylpantolactone which, followed by hydrolysis of the optically active O-acetylpantolactone, can be used to produce optically active pantolactone.

BRIEF DESCRIPTION OF THE DRAWING

The drawing is a phase diagram of temperature versus the percentage of D(−) or L(+) isomer.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, optically active pantolactone can be easily obtained in the following manner.

Racemic pantolactone can be acetylated to give a racemic O-acetylpantolactone by any standard state of the art method, and then it is directly resolved to optically active lactones, D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone, in a binary system. Further the optically active lactones are then deacetylated by hydrolysis with a diluted mineral acid to provide the optically active pantolactone.

With regard to O-acetylpantolactone, it is stated in the literature (J.A.C.S. 62, 2665 (1941)) merely that only one D(−)-O-acetylpantolactone has been isolated as crystals (M.P. 44°–45° C. and $[\alpha]_D^{29}$ −13.1° (C.=2.27, 95% ethanol). However, the D(−)-O-acetylpantolactone reported was synthesized by the acetylation of optically active D(−)-pantolactone. No process for the optical resolution of racemic O-acetylpantolactone has been disclosed.

The most characteristic or unique point of this invention is the fact that the optical resolution by the application of selective crystallization is carried out in a binary system. No process has been heretofore known for optical resolution in a binary system which does not use a resolving agent or solvent for selective crystallization.

The inventors have found that a homogeneous liquid phase composed of two optical isomers, D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone, can be resolved by selectively seeding with either optically active isomer thereof in a binary system at a temperature below 13.5° C. They have also found that this process is possible in a binary system only when a considerable difference exists between the melting point of the racemic mixture as a whole and the melting point of each optically active isomer contained therein. Further (at the same time) high stability of the mutually dissolved liquid of [illegible] isomers is required in the supercooled state.

More particularly, illustrating resolution in a binary system, FIG. 1 shows a phase diagram for a pair of optical isomers of O-acetylpantolactone.

For instance, after melting the racemic [illegible] at temperature A which is higher [illegible] temperature [illegible]

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the melting point of the racemic mixture, supercooling the racemic mixture melt down to temperature B (which is still below the melting point of the racemic mixture) and seeding selectively with seed crystals of, for example, D(−)-O-acetylpantolactone, with stirring, D(−)-O-acetylpantolactone begins to crystallize. As the crystallization proceeds, the liquid composition of the binary system is converted from point B to point C.

In the case of the resolution of a mixture (not the racemic mixture) which includes either active isomer more than the antipode, the same operation is applicable as in the case of FIG. 1, i.e., where line A′-B′-C′ shows this case, namely seeding the L-excess mixture liquid with L-isomer.

Upon progressing with crystallization of the desired isomer in a binary system, a proportion of the both D- and L-components will reach such a point as to result in a supersaturated state of the unseeded isomer and at this stage one cannot keep the system in the liquid phase. In a binary system, therefore, it is preferable, in an industrial resolution, to stop the crystallizing just before the absolute value of the optical rotation of binary system is about to decrease. In other words, the absolute value of the optical rotation of the system is an indication of the maximum amount of an isomer that can be crystallized from the system. As an example, assuming the value of the optical rotation of the homogeneous liquid phase to be zero, as one isomer is crystallized form the system, the absolute value of the optical rotation value of the homogeneous liquid phase will increase only so long as the isomer is being crystallized out since once the maximum crystallization is reached, the absolute value of the optical rotation will no longer increase. For instance, such optically active crystals having an absolute value of a specific rotation of 12.5°–13.5° (optical purity=89–96%) may be obtained, if the split crystals are collected when the absolute value of the optical rotation of the binary system reaches its maximum point. To control the crystallization, the maximum point of rotation in a binary system is continuously checked during performance of crystallizing resolution.

For the purpose of making filtration easy, it is preferable to add a small amount of organic solvent to the binary system either before crystallizing resolution or after crystallizing. As such an organic solvent, one which is soluble in O-acetylpantolactone may be utilized. For example, alcohols such as methanol, ethanol, or isopropanol, ethers such as ethylether, n-propylether or isopropylether, halogeno hydrocarbons such as dichloroether, dichloroethane or trichloroethylene, aromatic hydrocarbons such as benzene, xylene or toluene, amides such as dimethylformamide or acetoamide, ketones such as acetone or methylethylketone, esters such as ethyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate, isoamyl acetate or isopropyl acetate, aqueous organic solvents thereof, or mixtures of solvents thereof, are applicable to this purpose.

For adding such a solvent before crystallizing resolution, the amount of such a solvent which is added should be not more than 35% of the liquid phase, by weight. If the amount is more than 35%, it causes an undesirable extreme stabilization of the liquid system in its supercooled state, and consequently, the yield of the resolution may be reduced.

This feature of a binary system is fundamentally different from a ternary system which uses a great amount of solvent for selective crystallization. In the present invention the amount of solvent added must be limited to the extent of merely reducing the viscosity of the binary phase.

With regard to seeding crystals of optically active O-acetylpantolactone, the finer the particle size, the more suitable it is for resolution. Effective resolution may be carried out with seeding crystals in an amount of less than 5%, based on the whole homogeneous liquid phase.

The collected crystals of O-acetylpantolactone thus resolved may be further purified by washing or recrystallization from a suitable solvent (such as isopropylether) to provide pure crystals having an absolute optical rotation value of more than 13.7° (optical purity; more than 98%).

The hydrolysis of the resolved O-acetylpantolactone is carried out by refluxing it with mineral acid in the usual manner for hydrolysis. Optically active pantolactone can be obtained from the reaction solution by extracting with a suitable solvent such as dichloroethane, after neutralization and removal of acetic acid and water.

One starting material, DL-O-acetylpantolactone, for carrying out the resolution of this invention is prepared by the reaction of DL-pantolactone with an equivalent or greater than equivalent volume of acetic anhydride or acetyl chloride. The acetylated mixture is distilled under reduced pressure to give racemic O-acetylpantolactone (B.P. 130°–135° C./10 mm. Hg. M.P. 13.5° C.) at a high yield.

The present invention will be illustrated with more particularity by the following examples.

EXAMPLE 1

1300 g. of racemic pantolactone was dissolved in 1530 g. of acetic anhydride and the mixture was boiled with reflux for three hours. After acetic acid and excessive acetic anhydride were removed, the residue was distilled under reduced pressure to obtain 1620 g. of racemic O-acetylpantolactone. (Yield: 94.2%, B.P. 125°–130° C./10 mm. Hg.)

The purity of O-acetylpantolactone, by titration of the acetyl groups, showed to be 100%. In the same manner D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone were obtained. (Yield: 92–95%, $[\alpha]_D^{25}-14°$, and $[\alpha]_D^{25}+14.0°$).

10 g. of D(−)-O-acetylpantolactone having an $[\alpha]_D^{25}-14.0°$ was added to 200 g. of racemic O-acetylpantolactone as obtained above. The mixture was dissolved by heating, was cooled to 9–10° C., and then the mixture was seeded with 1.0 g. of D(−)-O-acetylpantolactone having an $[\alpha]_D^{25}-14.0°$ with stirring. After 1.75 hours, crystals were collected by filtration to obtain 23.0 g. of crystals having an $[\alpha]_D^{25}-12.8°$. 20.0 g. of the above-obtained crystals were washed with 14 ml. of isopropylether at a temperature of 4–6° C. to give 18.1 g. of precipitate having an $[\alpha]_D^{25}-13.8°$.

Further, racemic O-acetylpantolactone was added to the filtrate in the amount of 2.00 g., and the mixture was then dissolved with heating. After cooling to 9–10° C. the mixture was seeded with 1.0 g. of L(+)-O-acetylpantolactone ($[\alpha]_D^{25}+14.0°$) with stirring. After two hours, the crystals were collected by filtration to obtain 23.9 g. of crystals having an $[\alpha]_D^{25}+13.1°$.

Twenty g. of these crystals were washed with 10 ml of isopropylether at a temperature of 4–6° C. to give 18.0 g. of crystals having an $[\alpha]_D^{25}+13.9°$.

Ten g. of D(−)-O-acetylpantolactone having an $[\alpha]_D^{25}-13.9°$ obtained from the above process was boiled under reflux with 10 ml. of 1.0% aqueous hydrochloric acid for 1.5 hours. The resulting water, acetic acid and hydrochloric acid were distilled off under reduced pressure. The residue was cooled to room temperature to obtain 7.3 g. of white crystals. The yield was 97%, $[\alpha]_D^{25}-48.5°$ (c.=2, water). The purity of the pantolactone was 99.5%, by an acid-base titration.

Ten g. of L(+)-D-acetylpantolactone having an $[\alpha]_D^{25}+13.9°$ were boiled under reflux with 10 ml. of 1.0% sulfuric acid for 1.5 hours. The reaction mixture was then neutralized with sodium carbonate to a pH of 6.0 and water was distilled off under reduced pressure. The residue was extracted with dichloroethane and the solvent was removed to give 6.9 g. of L(+)-pantolactone having an $[\alpha]_D^{25}+48.8°$. The yield was [illegible] (purity: 98.8%).

EXAMPLE 2

The mixture of 200 g. of racemic O-acetylpantolactone, 10 g. of D(−)-O-acetylpantolactone having an $[\alpha]_D^{25}-14.0°$ synthesized in Example 1 and 30 ml. of isopropylether was cooled up to 4°-5° C., and the mixture was seeded with 1.0 g. of D(−)-O-acetylpantolactone having an $[\alpha]_D^{25}-14.0°$, with stirring. After two hours, crystals were collected by filtration to obtain 24.0 g. of crystals having an $[\alpha]_D^{25}-12.9°$.

EXAMPLE 3

Eighteen ml. of 80% aqueous isopropylalcohol were added to 200 g. of racemic O-acetylpantolactone as synthesized in Example 1. The mixture was cooled to 0° C., and then seeded with 1.0 g. of L(+)-O-acetylpantolactone having an $[\alpha]_D^{25}+14.0°$, with stirring. 2.5 hours after seeding, 12.0 g. of crystals having an $[\alpha]_D^{25}+13.0°$ were obtained.

What is claimed is:

1. A method for the optical resolution of a homogeneous liquid phase composed of D(−)-O-acetylpantolactone and L(+)-O-acetylpantolactone which comprises selectively seeding said homogeneous liquid phase with optically active seed crystals of either of the two isomers at a temperature below 13.5° C. to thereby crystallize the same isomer as the seed crystals, and recovering the precipitate.

2. The method according to claim 1 in which the resolution is carried out by the addition of less than 35% by weight, based upon the weight of the homogeneous liquid phase, of a solvent in which O-acetylpantolactone is soluble selected from the group consisting of alcohols, ethers, halogenated hydrocarbons, aromatic hydrocarbons, amides, ketones, esters and mixtures thereof.

3. The method according to claim 1 further comprising adding to the product of the selective seeding operation, prior to the recovering step, a solvent in which O-acetylpantolactone is soluble selected from the group consisting of alcohols, halogenated hydrocarbons, aromatic hydrocarbons, amides, ketones, esters and mixtures thereof.

4. The method according to claim 2 where the solvent is selected from the group consisting of methanol, ethanol, isopropanol, ethylether, n-propylether, isopropylether, dichloroethane, trichloroethylene, benzene, xylene, toluene, dimethylformamide, acetoamide, acetone, methylethylketone, ethyl acetate, n-propyl acetate, isobutyl acetate, n-butyl acetate, isoamyl acetate, isopropyl acetate, mixtures of water and said solvents, and mixtures thereof.

5. The method according to claim 3 wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, ethylether, n-propylether, isopropylether, dichloroether, dichloroethane, trichloroethylene, benzene, xylene, toluene, dimethylformamide, acetoamide, acetone, methylethylketone, ethylacetate, n-propylacetate, isobutylacetate, n-butylacetate, isoamylacetate, isopropylacetate, mixtures of water and said solvents, and mixtures thereof.

6. The method according to claim 1 wherein said seed crystals are added in an amount of less than 5% by weight, based upon the weight of the entire homogeneous liquid phase.

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3,038,937 6/1962 Cave .... 260—534 G

ALEX MAZEL, Primary Examiner

JOSE TOVAR, Assistant Examiner

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STABILITY OF CALCIUM PANTOTHENATE IN PREMIX

EXHIBIT G

Producer of d-CALCIUM PANTOTHENATE USP 20th.

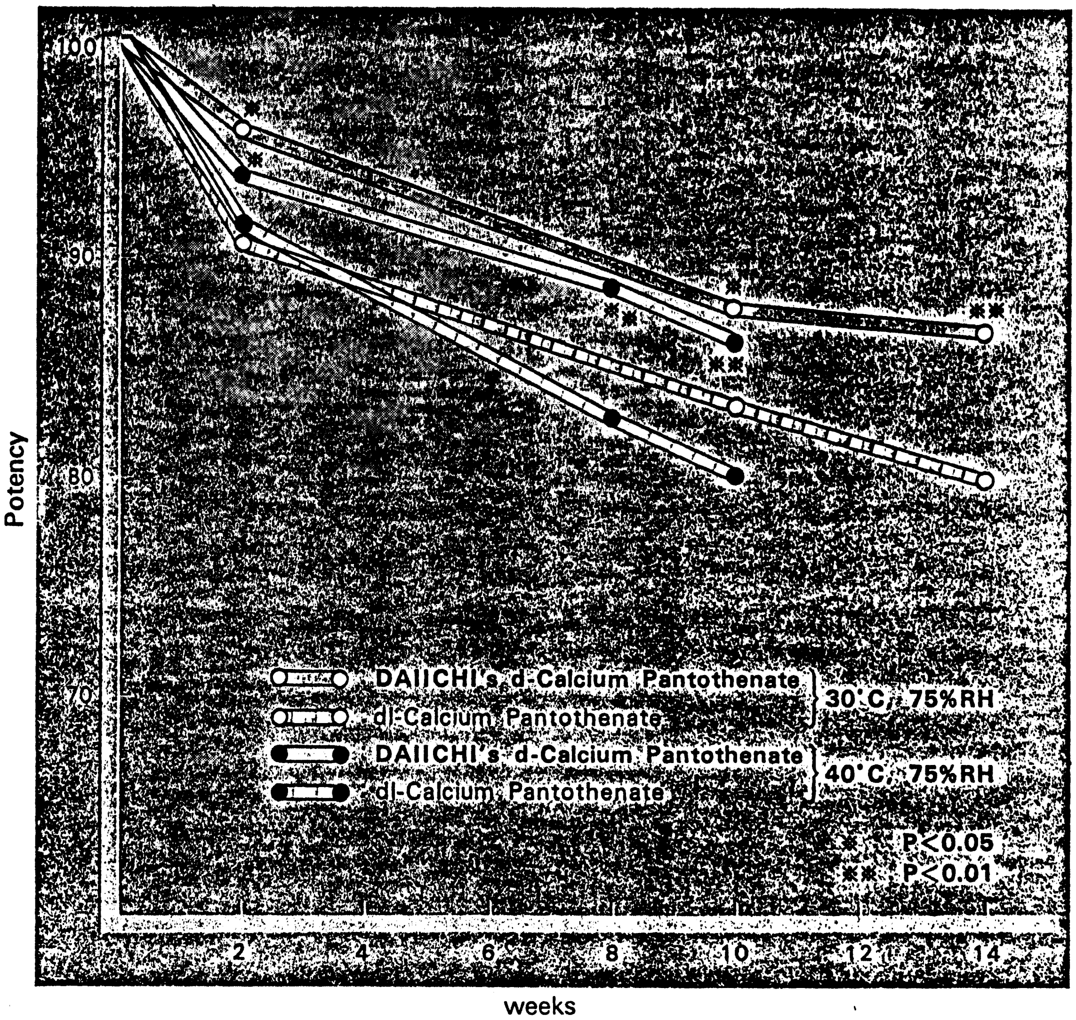
DAIICHI SEIYAKU CO., LTD.

DAIICHI

14-10, Nihonbashi 3-chome, Chuo-ku, Tokyo, 103 Japan.

STABILITY OF CALCIUM PANTOTHENATE

Time-lapse change of the potency of d-and dl-Calcium Pantothenate (abbreviated as Calpan) in premix was measured under various conditions by microbiological method specified in USP.



At 75%RH, reduction of the potency was observed in both d-and dl-Calpan. However the reduction in d-Calpan was less than that in dl-Calpan significantly.

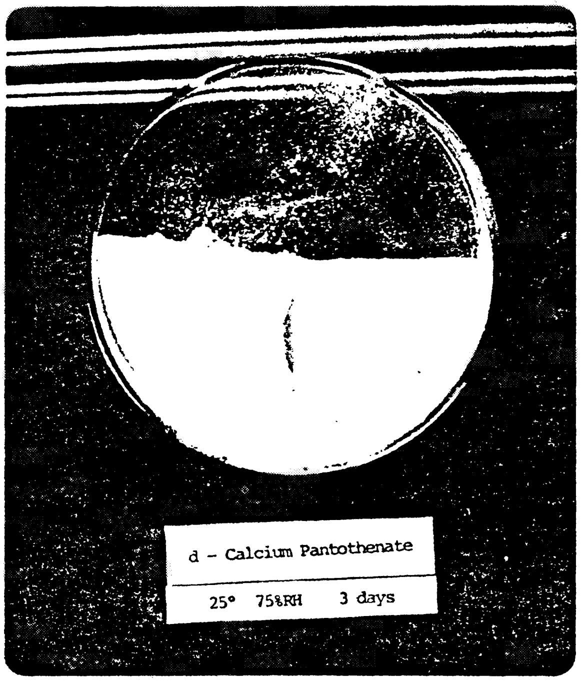
This is mostly attributed to the difference of hygroscopicity.

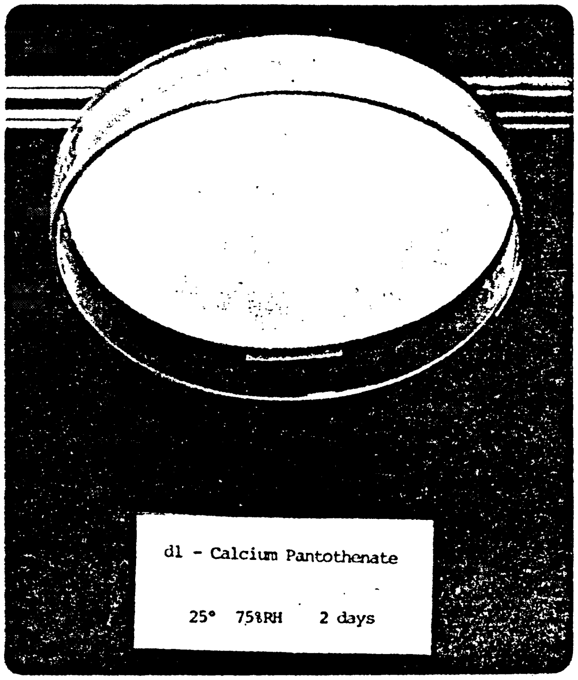
MOISTURE ABSORPTION OF PREMIX

	2	4	6	10	weeks
d	**3.6%**	**1.9%**	**1.9%**	**1.5%**	
dl	**4.5**	**5.5※※**	**4.2**	**4.2※※**	

Premix containing DAIICHI's d-Calpan was less hygroscopic, measured at 30°C, 75%RH.

HYGROSCOPICITY OF CALPAN





	24 hr	48 hr
d	**6.0%**	**8.0%**
dl	**10.1**	**Hardened**

A single d-Calpan of DAIICHI was also less hygroscopic.

* Ingredients of Premix

	grms.
Thiamine Nitrate	2.0
Riboflavin	10.0
Pyridoxine	2.0
Nicotinamide	2.0
Choline Chloride	138.0
Folic acid	1.0
d-Calcium Pantothenate	4.35 (dl : 9.57)
Soybean meal	840.65 (835.43)
	1000.0

REQUIREMENT

Species	grams/ton·feed
Chickens	10 – 20
Turkeys	10 – 20
Swine	12 – 20
Calves	12
Horses	10 – 50
Pets	10 – 20

The quantity should be increased under stress conditions.

INCOMING

TELEGRAM

American Embassy TOKYO

755

EXHIBIT H

ACTION:
CML-7
INFO:
AMB
DCM
A/EX
POL
POL/A
LAB
E/C
E/MIN
CML
USTC
USTS
FINATT
MDO
AGRIC
DAO
DEA
LEGAT
CUST
SCI
POE
NSR
ISF
MARAD
ADMIN
GSO

VV TKO620
CO RUFHKO UNCLASSIFIED
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O 160113Z NOV 79
FM AMCONSUL OSAKA KOBE
TO RUEHDC/USDOC WASHDC IMMEDIATE
INFO RUEHKO/AMEMBASSY TOKYO 7881
BT
UNCLAS OSAKA KOBE 1296

E.O. 12065: N/A
TAGS: BEXP, JA
SUBJECT: WTDR/FTI: ALPS PHARMACEUTICAL

REF: USDOC 16084

1. JAPAN
OFFICE USE: 2. 588 3. NA 4. 04
5. ALPS PHARMACEUTICAL CO., LTD. (ALPS YUKUHIN KOGYO K.K.)
6. 2-10-50 MUKAI-MACHI, FURUKAWA-CHO
7. YOSHIKI-GUN, GIFU PREFECTURE 509-42
8. CONTACT: GENZO OGURA
9. TITLE: PRESIDENT
10. PHONE: 05777/32021 11. TELEX: 222 5248 ALPSTK J
12. CABLE: ALPSPHARMACO TOKYO
13. ESTABL: 1947 14. EMPL: 206 15. SIZE: MEDIUM
16. REPUTATION: Y-GOOD 17. RPT DATE: 11/79
OFFICE USE: 18. NA 19. NA 20. NA 21. NA 22. NA
23A. 28331/M04 MFR. & EXP. OF SYNTHETIC ORGANIC MEDICIANL CHEMICALS.
23B. 28332/M04 MFR. & EXP. OF PHARMACEUTICAL RAW MATERIALS.
24. FOREIGN SALES: EUROPE 50 PCT, USA 20 PCT, CANADA 5 PCT, SOUTHEAST ASIA 12 PCT, SOUTH AMERICA 5 PCT.
25. FINANCIAL REFS: SUMITOMO BANK, GIFU BRANCH, 7-9 KANDA-CHO, GIFU 500; TOKAI BANK, GIFU BRANCH, 3 KANDA-CHO, GIFU 500; JUROKU BANK, FURUKAWA BRANCH, 2-23 MINO-MACHI, FURUKAWA-CHO, YOSHIK-GUN, GIFU PREFECTURE 509-42.
26. TRADE REFS: NONE
27. FOREIGN FIRMS REPRESENTED: NONE
28. POST EVALUATION: THIS FIRM IS ONE OF THE LEADING MANUFACTURERS OF PHARMACEUTICAL RAW MATERIALS AND FINE CHEMICALS IN JAPAN. PAID-IN CAPITAL STANDS AT YEN 90 MILLION. (US DOL ONE EQUALS TO YEN 245 AT PRESENT.) PRESIDENT GENZO OGURA (AGE 64) OWNS 50 PCT OF THE FIRM'S SHARES. THE FIRM MAINTAINS A HEAD OFFICE AND TWO PLANTS IN FURUKAWA-CHO, GIFU HAVING A TOTAL FLOOR SPACE OF 13,000 SQUARE METERS ON PLOTS TOTALING 46,000 SQUARE METERS. BRANCHES ARE LOCATED IN TOKYO AND OSAKA. IT CLAIMS SALES DURING THE YEAR ENDING MARCH 1979 OF YEN 5,000 MILLION. ABOUT 60 PCT OF ITS PRODUCTION IS EXPORTED DIRECT OR THROUGH TRADING FIRMS. PRINCIPAL PRODUCTS INCLUDE BERBERIN CHLORIDE, RUTIN, SCOPOLAMINE BUTYLBROMIDE, CALCIUM PANTOTHENATE AND PHENYLPROPANOLAMINE HYDROCHLORIDE, AND THEY ARE SOLD MOSTLY TO PHARMACEUTICAL MANUFACTURERS. THE FIRM IMPORTS MEDICAL HERBS AND CRUDE DRUGS FROM PEOPLE'S REPUBLIC OF CHINA, SOUTHEAST ASIA, PAKISTAN, AUSTRALIA, WEST GERMANY AND SOUTH AMERICA.
A LOCAL BANKING SOURCE REPORTS THAT THE FIRM'S SALES IN FY 1979 WILL AMOUNT TO YEN 6,000 MILLION WITH AFTER-TAX PROFIT OF ABOUT YEN 400 MILLION, AND THAT THE FIRM ENJOYS A GOOD REPUTATION. THE BANK CONSIDERS IT RELIABLE FOR ITS ORDINARY BUSINESS ENGAGEMENTS.
THE CONSULATE GENERAL RECOMMENDS THE FIRM AS A SUITABLE TRADE CONTACT FOR INTERESTED U.S. FIRMS.

EXHIBIT I

Premixers

Hoffmann-LaRoche, Inc.
340 Kingsland Street
Nutley, N.J. 07110
201-235-2461
Sal Guidone, Director of Purchasing

Quali-Tech Products, Inc.
318 Lake Hazeltine Drive
Chaska, MN 55318
612-448-5151
Delbert L. Ploen, President

Stutts Scientific Service, Inc.
310 West B Street
P. O. Box 72
Ontario, CA 91761
714-988-8222
Dr. E. C. Stutts, President

Mountaire Feeds, Inc.
124 East 5th Street
P. O. Box 5391
North Little Rock, Arkansas 72119
501-376-6751
Wayne Brock, Vitamin Premix Manager

Henwood Feed Additives
211 Western Road
P. O. Box 577
Lewisburg, Ohio 45338
Walter H. Henwood, President

Carl S. Akey, Inc.
State Route 503, South
P. O. Box 607
Lewisburg, Ohio 45338
513-962-2661
Carl S. Akey, President

V.P.O., Inc.
4444 South 76th Street
Omaha, Nebraska 68127
402-339-4900
W. L. Winstrom, President

Cadco, Inc.
10100 Douglas
P. O. Box 3599
Des Moines, Iowa 50322
515-276-5417
Don Heggen, President

Dawe's Laboratories, Ltd.
Current Address: 450 State Street
Chicago Heights, IL 60411
312-757-6000
After April 1: 7100 North Tripp Ave.
Chicago, IL 60646
(New phone number not known)

International Nutrition, Inc.
6664 "L" St.
Omaha, Nebraska 68117
402-331-0123
Dr. Richard J. Danke, President