UNITED STATES TARIFF COMMISSION

AMPICILLIN

Report to the President on
Preliminary Inquiry into Complaint
Under Section 337 of the Tariff Act of 1930

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UNITED STATES TARIFF COMMISSION

Address all communications to

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C O N T E N T S

Introduction

On January 27, 1970, Beecham Group Limited 1/ and Beecham, Inc., 2/ of Clifton, New Jersey, hereinafter referred to as complainants, filed a complaint with the United States Tariff Commission requesting relief under section 337 of the Tariff Act of 1930, as amended (19 U.S.C. 1337), alleging unfair methods of competition and unfair acts in the importation and sale of the drug ampicillin. Complainants alleged that claim 5 of U.S. Patent No. 2,985,648 3/ owned by Beecham Group Limited specifically covers ampicillin, and that the importation and sale of the drug by Zenith Laboratories, Inc., of Northvale, New Jersey, hereinafter referred to as respondent, has the effect or tendency to destroy or substantially injure an efficiently and economically operated industry in the United States.

Notice of receipt of the complaint and the initiation of the preliminary inquiry was published in the Federal Register (35 F.R. 3139-40) February 18, 1970. Interested parties were given until March 30, 1970, to file written views pertinent to the subject matter. Upon written request of the named respondent, the Commission extended the time for filing written views until May 29, 1970. Copies of the complaint, the notice of investigation, and the extension of time for filing written views were served upon all known interested parties.

1/ Beecham Group Limited is a limited company (corporation) of Great Britain engaged in part in the business of research for, discovery, evaluation, development, manufacture and marketing of therapeutic products, including ampicillin.

2/ Beecham, Inc., is an approximately 90% owned subsidiary of Beecham Group Limited and it is engaged in the manufacture and sale of various therapeutic products including ampicillin.

3/ A copy of the patent is attached as Appendix A.

The Commission conducted a preliminary inquiry, in accordance with section 203.3 of the Commission's Rules of Practice and Procedure (19 C.F.R. 203.3) to determine whether a full investigation is warranted and, if so, whether it should recommend to the President that a temporary exclusion order be issued pursuant to 19 U.S.C. 1337(f). The standard adopted by the Commission for deciding whether the issuance of such an order should be recommended (as indicated to the parties by letter notice) is whether the complainant has made a prima facie showing of violation of the provisions of section 337 of the Tariff Act of 1930, and whether, in the absence of a temporary order of exclusion, immediate and substantial injury would be sustained by the domestic industry involved.

Alleged Unfair Methods of Competition and Unfair Acts

Alleged Patent Violation

Complainants allege that claim 5 of U.S. Patent No. 2,985,648 issued to Frank P. Doyle, John H.C. Nayler, and Harry Smith on May 23, 1961, and by mesne assignment now owned by Beecham Group Limited, specifically covers ampicillin and is being infringed by the importation into, and sale in, the United States of Ampicillin. Said Patent No. 2,985,648 covers the invention of certain new penicillins, sometimes called alpha-aminobenzyl penicillins, in the field of semi-synthetic penicillins. One of the several penicillins of said Patent ("D-(-)-alpha-aminobenzyl penicillin") is known by the generic name ampicillin. This is a "composition of matter" patent under 35 U.S.C. Sec. 101 which is limited to 17 years; it expires in May 1978.

Beecham Group Limited, through a subsidiary, entered into a license agreement covering Patent No. 2,985,648 with Bristol Laboratories, Inc., effective April 2, 1959, and a supplemental agreement with Bristol-Myers Company, effective August 1, 1960. Pursuant to these agreements, Bristol-Myers was given the right to produce and sell ampicillin and to license others to do so under the patent. Bristol-Myers commenced the manufacture and sale of ampicillin in the United States late in 1963. It has issued sub-licenses to American Home Products Corp., of Westchester, Pennsylvania, and to Squibb-Beechnut, Inc., of New Brunswick, New Jersey; the sub-licensees commenced the manufacture and sale of ampicillin in the United States in 1966 and 1967, respectively. In addition, Parke Davis & Company has purchased ampicillin from Bristol-Myers since 1968, and it is now selling ampicillin in the United States. Beecham, Inc., has since late 1964 been engaged in the manufacture and sale of ampicillin in the United States.

Respondent's Answer and Intervention of Department of Justice

In its answer filed with the Commission May 28, 1970, respondent admits that it has purchased ampicillin since March 1969, from Anker-farm S.p.A. in Milan, Italy, and marketed it throughout the United States as alleged in the complaint. Respondent alleges, however, that the patent is invalid because it was obtained by fraud on the Patent Office and is unenforceable because of patent misuse, citing Sections 1

and 2 of the Sherman Act. Similar claims of violations of Sections 1 and 2 of the Sherman Act and patent invalidity and misuse form the basis for respondent's counterclaim to a patent infringement action instituted May 7, 1969, in the United States District Court of New Jersey by complainant, Beecham Group Limited.

After the complaint was filed with the Tariff Commission, the Department of Justice on March 19, 1970, filed a civil antitrust suit charging violation of Sections 1 and 2 of the Sherman Act against the complainants and Bristol-Myers Company (a licensee of Beecham Group Limited). The Justice Department complaint alleges that the defendants combined and conspired in unreasonable restraint in trade in ampicillin and other semi-synthetic penicillins by, among other things, fraudulently procuring and enforcing Beecham Group Limited's U.S. Patent No. 2,985,648; restraining and preventing the sale of semi-synthetic penicillins in bulk form; restraining and preventing the sale of semi-synthetic penicillins under other than specified trade names.

July 22, 1970, the Judicial Panel on Multidistrict Litigation entered an opinion and order in the ampicillin antitrust litigation. Pursuant to 28 U.S.C. § 1407, the Beecham Group Limited v. Zenith Laboratories, Inc., D.N.J., CA No. 526-69 action has been coordinated and consolidated with the Department of Justice action, and along with a number of other suits, all cases have been assigned to the U.S. District Court for the District of Columbia.

Both respondent and the Department of Justice have requested the Commission to exercise its discretion and defer making any recommendation under Section 337 pending the outcome of the Justice Department suit.

Findings and Recommendations of the Commission

Upon conclusion of its preliminary inquiry the Tariff Commission, on September 25, 1970, ordered a formal investigation. The Commission was unanimous on that order, but was equally divided (2-2) on the question of whether to recommend to the President that he issue a temporary exclusion order to forbid entry of ampicillin and any products containing ampicillin in accordance with the provisions of section 337(f), until the investigation ordered is completed. 1/ Pursuant to section 330(d)(1) of the Tariff Act of 1930, as amended (19 U.S.C. 1330(d)(1)), 2/ both recommendations are forwarded to the President.

1/ Commissioners Clubb and Moore recommend the issuance of a temporary exclusion order and Presiding Commissioner Sutton and Commissioner Leonard do not so recommend. Separate statements begin on pages 6, 19, and 20, respectively.

2/ Sec. 330(d)(1) of the Tariff Act of 1930, as amended, provides that--

> Whenever, in any case calling for findings of the Commission in connection with any authority conferred upon the President by law to make changes in import restrictions, a majority of the commissioners voting are unable to agree upon findings or recommendations, the findings (and recommendations, if any) unanimously agreed upon by one-half of the number of commissioners voting may be considered by the President as the findings and recommendations of the Commission: Provided, that if the commissioners voting are divided into two equal groups each of which is unanimously agreed upon findings (and recommendations, if any) the findings (and recommendations, if any) of either group may be considered by the President as the findings (and recommendations, if any) of the Commission. In any case of a divided vote referred to in this paragraph the Commission shall transmit to the President the findings (and recommendations, if any) of each group within the Commission with respect to the matter in question.

Statement of Commissioners Clubb and Moore

On January 27, 1970, Beecham Group, Ltd., a British corporation (hereinafter "Beecham"), and its U. S. subsidiary, Beecham Inc., filed a petition with the United States Tariff Commission under section 337 of the Tariff Act of 1930 asking, inter alia, that the Commission recommend to the President that certain imported pharmaceuticals be barred from entry into the United States pending the completion of the Commission's investigation to determine whether they should be permanently barred. For the reasons set out below, we agree that a Temporary Exclusion Order should be issued.

The relevant facts are as follows. In 1961, Beecham obtained a United States patent on the drug Ampicillin. Thereafter, Beecham authorized its U. S. subsidiary, Beecham Inc., its licensee and sublicensees [1/] to manufacture Ampicillin in the United States.

In March 1969, Zenith Laboratories, Inc., without obtaining a license from Beecham, began importing Ampicillin from Italy, a country which does not grant patents on pharmaceuticals. On May 7, 1969, Beecham filed a patent infringement suit against Zenith, [2/] charging that the unlicensed sale of Ampicillin in the United States

1/ Bristol-Myers Company is the principal licensee. Sublicenses have been granted to Squibb-Beechnut, Inc., and the Wyeth Division of American Home Products Corporation.

2/ Beecham Group, Ltd., v. Zenith Laboratories, Inc., D. N. J. CA No. 526-69.

by Zenith infringed Beecham's United States patent. Zenith answered that Beecham's patent was invalid, and that, even if valid, it should not be enforced because of Beecham's alleged misuse of the patent. At this writing, this suit was still in the discovery stage.

On March 19, 1970, the Department of Justice filed a civil antitrust suit under sections 1 and 2 of the Sherman Act against Beecham, its U. S. subsidiary and its licensees alleging, inter alia, that they had conspired to restrain trade in Ampicillin. 3/ As of this date, this suit has not gone to trial.

On January 27, 1970, this proceeding was begun when Beecham and Beecham Inc. filed a complaint with the Tariff Commission alleging that Zenith's unlicensed importation of Ampicillin constituted an unfair method of competition and an unfair act under section 337 of the Tariff Act of 1930. 4/ Petitioners accordingly asked that the

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3/ U.S. v. Bristol-Myers Co., et al, D.D.C., CA No. 822-70.

4/ Section 337 reads in pertinent part as follows:

> Unfair methods of competition and unfair acts in the importation of articles into the United States, or in their sale by the owner, importer, consignee, or agent of either, 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, are declared unlawful, and when found by the President to exist shall be dealt with, in addition to any other provisions of law, as hereinafter provided. 19 U.S.C. §1337a (1964).

Commission recommend to the President that an Exclusion Order be issued prohibiting the further unlicensed importation of Ampicillin. Petitioners also requested that the Commission recommend to the President that a Temporary Exclusion Order be issued, pending final disposition of the matter by the Tariff Commission and the President. The Department of Justice, on the other hand, has requested that the Commission suspend its section 337 investigation until the Federal Courts have disposed of the Department's antitrust suit seeking cancellation of Beecham's patent. 5/

The issue now before the Commission is whether to suspend the proceedings as requested by the Department of Justice, and, if not, whether to recommend to the President that a Temporary Exclusion Order be issued. For the reasons set out below we deny the Department of Justice request to suspend, and recommend that a Temporary Exclusion Order be issued.

The Department of Justice Request

The Commission has received two communications from the Department of Justice asking that the Commission suspend its section 337 proceedings until the Federal Courts have disposed of the Department's antitrust suit against petitioners.

5/ Letter from Assistant Attorney General McLaren to U. S. Tariff Commission Secretary Mason dated June 1, 1970.

In its first letter dated June 1, 1970, the Department stated that

> "We believe that the charges in the Government's antitrust suit bear directly on the issues of 'unfair methods of competition' and 'industry, efficiently and economically operated' under the Act and strongly support withholding of any recommendation under Section 337 until the Government's suit has been resolved."

Accordingly, it requested that the Commission "exercise its discretion and defer making any final recommendation on Beecham's complaint."

In a second letter dated September 18, 1970, the Department stated that it was not asking that the Commission relinquish jurisdiction over the Beecham complaint.

> "The request by this Department is rather that the Commission respect the principle of comity between different agencies of the Government by timing the exercise of its jurisdiction so as not to impede or embarrass the functioning of a sister agency. * * *
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> "In the present case, if the Commission were to recommend that an exclusion order be issued and the Department of Justice subsequently won its lawsuit, the Commission's action would, in effect, be overturned. The harm resulting to the public in the meantime could not, however, be repaired. It would seem unwise for the Tariff Commission to recommend to the President that he issue an exclusion order based upon a patent at the same time that that patent is being challenged by another Government agency on grounds of fraud."

These letters appear in effect to be a request that the Commission suspend its patent-based section 337 proceeding until the

validity or enforceability of the patent can be decided by a Federal Court.

Similar requests have frequently been made in the past, and have sometimes been granted by the Commission. 6/ Our reviewing court (the Court of Customs and Patent Appeals) has ruled,

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6/ For example, in the section of the Commission's Annual Report for 1937 which discusses section 337 cases, the Commission said:

> Patent infringement was the principal ground of complaint and in practically all cases neither the validity nor the scope of the patents had been adjudicated. In such cases the Commission has declined to order formal investigations under section 337, and in two cases principally involving patents. . . it has dismissed investigations which had been previously ordered. 21 U.S.T.C. Ann. Rep. 36 (1937).

The Department of Justice also calls our attention to United States v. Singer Manufacturing Co., 374 U.S. 174, 188 (1963), in which the Supreme Court noted that the Commission had suspended its patent-based section 337 proceedings pending the outcome of antitrust litigation.

The Commission's report of its action in the Singer case reads in part as follows:

> On January 12, 1960, the Commission announced that it had decided to hold in abeyance its decision, pending the outcome of an antitrust action filed by the Department of Justice against the Singer Manufacturing Co., on December 22, 1959, in the U.S. District Court for the Southern District of New York. 47 U.S.T.C. Ann. Rep., pp. 26-27 (1963).

however, that such suspensions are not justified. Thus, in In re Von Clemm, the Court said

> It is urged by Von Clemm that the Tariff Commission should have refrained from acting in this case and that this court should also refrain from acting since the questions of validity of Linde's patent and infringement thereof by Von Clemm's stones are involved in a suit now pending between appellant and Linde in the United States District Court for the Southern District of New York. We are aware of no statute, however, which would justify, much less require, this court to ignore the provisions of section 337, supra, which we must necessarily regard as requiring timely disposition of appeals arising thereunder. In re Von Clemm, 229 F. (2d) 441, 445 (C. C. P. A. 1955).

We are bound by this ruling in the present case, 7/ but were we free to determine the matter for ourselves, the result would be the same. The effect of suspending the section 337 proceeding in this case would be to consider this patent invalid until the patentee had prevailed in the courts. This would put the burden of proof on the patentee, rather than on the party attacking the patent. We think this would be inconsistent with the thrust of legislation 8/ and

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7/ The only difference between the suspension requested here and that previously condemned by the C. C. P. A. in In re Von Clemm is that here the request is made by a Government agency in an antitrust suit rather than by a private litigant in a patent infringement action. But the objective of the private litigant and the Department is the same; i. e., to have the patent declared unenforceable.

8/ 35 U. S. C. §282 reads in part as follows:

> "A patent shall be presumed valid. The burden of establishing invalidity of a patent shall rest on a party asserting it."

court decisions 9/ requiring that patents be presumed valid until held invalid.

Accordingly, the Commission has unanimously denied the Department of Justice request that the proceedings be suspended.

9/ See e.g., In re Von Clemm, supra; In re Orion 71 F (2d) 458 (C.C.P.A. 1934); and Frischer & Co., (Inc.), et al v. U.S., 17 C.C.P.A. 494 (1930). In this latter case, the Court of Customs and Patent Appeals said,

> In short, when the complainant introduced its certified patents in evidence they should have been treated as prima facie evidence of their validity. Lehnbeuter v. Holthaus, 105 U.S. 94, 96; Fenton Co. v. Office Spec. Co., 12 App. D.C. 201, 216; Consol. Con. Co. v. Hassam Pav. Co., 227 Fed. 436; R.R. Sup. Co. v. Hart Steel Co., 222 Fed. 261, 274. If no such patents had been in fact issued, or if they had by their terms expired, or if some court of competent jurisdiction, whose judgment would be binding upon the commission, had held them to be invalid, and such facts had been shown, these circumstances might have been considered by the commission, if the existence of the patents was material to the inquiry. This, however, in our judgment, was as far as the commission could legally go in this respect. As no denial was made by respondents as to the issuance of the patents in question and no attack made upon them except that they were improvidently issued, they should have been treated as valid by the commission. Frischer & Co. (Inc.), et al. v. United States, 17 C.C.P.A. 494, 510 (1930).

Requirements for a Temporary Exclusion Order Recommendation

The next question is whether the Commission should recommend to the President that a Temporary Exclusion Order be issued in this case. The Commission has informally ruled in past cases that a Temporary Exclusion Order should be recommended (1) if the petitioner has established a prima facie case in the preliminary investigation and (2) if the petitioner will suffer an immediate and substantial injury in the absence of a Temporary Exclusion Order.

Prima Facie Case

In order to establish a prima facie case under section 337, it is necessary to show that, based upon the facts presently available to the Commission, there is every reason to believe that the actions of the respondent violate section 337.

Respondent has violated section 337 if the acts complained of

(1) amount to an "unfair method of competition" or an "unfair act", and

(2) have the effect or tendency to

(a) substantially injure an efficiently and economically operated domestic industry, or

(b) prevent the establishment of a domestic industry, or

(c) restrain or monopolize commerce.

There can be no doubt that a prima facie showing has been made that respondent is violating section 337. Respondent concedes that it is importing without license a product patented in the United States by petitioner. The Commission and the courts have long held that such importations are an unfair method of competition within the meaning of section 337. 10/

Similarly, there can be no doubt that the unlicensed importations have the tendency to substantially injure Beecham and its licensees, which together make up the domestic industry producing Ampicillin. 11/ The U.S. patentee must recover its research

10/ In Self-Closing Containers (Squeeze-Type Coin Purses), U.S.T.C. Inv. No. 337-18 (1962), the Commission stated:

> If an article manufactured in a foreign country is made in accordance with, embodies, employs, or contains the invention disclosed in a current United States patent that has not been held invalid by a court of competent jurisdiction, it is an unfair method of competition or unfair act, within the meaning of section 337 of the Tariff Act of 1930, to import such article into the United States or sell it domestically without license from the registered owner of the patent. This determination is in accord with the applicable decisions of the United States Court of Customs and Patent Appeals. See, In re Von Clemm, 229 F. 2d 441, 443 (1955); In re Orion Co., 71 F. 2d 458, 465 (1934); and In re Northern Pigment Co., 71 F. 2d 447, 455 (1934). See also, Frischer & Co., Inc. v. Bakelite Corp., 39 F. 2d 247 (1930).

11/ In patent-based section 337 proceedings, the "industry" involved is the industry which is legally entitled to manufacture and sell the patented articles. In the Ear Hearing Aids, Inv. No. 337-20, (July 1966) pg. 20; Squeeze-Type Coin Purses, Inv. No. 337-18, (April 1965) pg. 8; Synthetic Star Sapphires, Inv. No. 337-13 (September 1954) pg. 20.

costs incurred in the development of Ampicillin, and the licensees must pay a royalty. These interests obviously will tend to be injured by a competing importer who is not burdened with either research costs or with royalty payments.

It is clear, therefore, that a prima facie showing of a section 337 violation has been made.

Immediate and Substantial Injury

In order to recommend a Temporary Exclusion Order, the Commission must also find that petitioners will suffer immediate and substantial injury in the absence of a Temporary Exclusion Order. It seems clear that they will. Ampicillin is already being imported in substantial quantities, and presumably each sale made by the unlicensed importers means lost sales and lost profits for Beecham, the patent holder of record, and its licensees. While it is not clear how large an inroad the unlicensed importer will ultimately make in the domestic Ampicillin market, there appears to be no economic reason why he should not dominate the market if he is given sufficient time.

And it seems clear that the Commission's investigation will take long enough so that the infringing importer, Zenith, will be given that time. The Commission enlarged its investigation in this case to include an inquiry into allegations of patent misuse and fraud

which have been raised by Zenith as a defense to the petitioner's charge of patent infringement. Although we disagree with our colleagues' conclusion that these issues are relevant in a section 337 proceeding 12/, we have agreed to this expansion because we believe that, within reason, the Commission should investigate any issue on which any Commissioner needs information in order to make his decision.

We fear, however, that the broadened scope of the Commission's investigation will significantly extend the time required to complete its investigation. The misuse issue, for example, centers around an alleged antitrust law violation. Such issues can take a long time to resolve under the best of circumstances and the additional issue of fraud further complicates the matter. If a Temporary Exclusion Order is not issued, respondent Zenith will be permitted to continue and expand its infringement of petitioner's patent during this period.

The only way the President can make section 337 effective under these circumstances is to issue a Temporary Exclusion Order, for if he does not, it is possible -- even likely -- that every respondent in a patent-based section 337 proceeding will allege misuse as a

12/ For our views on the relevance of patent misuse in a section 337 proceeding, see Furazolidone, Inv. No. 337-21 (November 1969), pp. 37-40.

defense, perhaps frivolously in some cases, knowing that he can go on infringing the petitioner's patent until the Commission's investigation has been completed -- and he can be assured that with such issues involved, it will be a lengthy proceeding. If the respondent can postpone the final decision until the patent has expired or nearly expired, he will have won in the marketplace even though he loses in the courts and the Commission.

Possible Entry Under Bond

It might be well to note here that the interests of the respondent are not ignored when a Temporary Exclusion Order is issued.

Section 337 provides that where a Temporary Exclusion Order has been issued, the excluded goods are still "entitled to entry under bond prescribed by the Secretary of the Treasury". 13/ Thus, the respondent may continue his importing business while the Commission's investigation is in progress provided he posts the required bond with the Secretary of the Treasury. If the respondent ultimately

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13/ The statute reads in pertinent part as follows:

> Whenever the President has reason to believe that any article is offered or sought to be offered for entry into the United States in violation of this section but has not information sufficient to satisfy him thereof, the Secretary of the Treasury shall, upon his request in writing, forbid entry thereof until such investigation as the President may deem necessary shall be completed; except that such articles shall be entitled to entry under bond prescribed by the Secretary of the Treasury. 19 U.S.C. §1337(f).

prevails, then the Temporary Exclusion Order is lifted, [14/] and the bond is no longer necessary. On the other hand, if a permanent Exclusion Order is issued, the Secretary may proceed against the bond covering the importations made during the pendency of the proceedings. [15/]

Conclusion

In short, it seems to us that if United States patents are to have a practical value they must be protected from unlawful international exploitation. Accordingly, we believe that it is desirable for the President to issue a Temporary Exclusion Order in a case of this type.

14/ Our reviewing court has said in a similar case,

> As pointed out in In re Orion Co., supra, any order which may be issued by the President may be corrected in the event of a subsequent holding of invalidity of a patent. Moreover, under section 337, supra, the President may, in his discretion, provide for entry of the disputed merchandise under bond pending, inter alia, final determination of the issues of validity and infringement. In re Von Clemm, 229 F. 2d 441 (C. C. P. A. 1955).

15/ 19 C.F.R. §25.4 (29); T.D. 454 74. C.f., Frischer & Co. Inc., et al, v. Elting, 60 F. 2d 711 (2nd Cir. 1932).

Statement of Presiding Commissioner Sutton

I concur with the other Commissioners that the facts obtained in the preliminary inquiry support the ordering of a full investigation; however, I do not concur with the recommendation for the issuance of a temporary exclusion order to forbid entry of ampicillin and any products containing ampicillin.

Although respondent admits importing and selling ampicillin, a product made in accordance with claim 5 of complainant's U.S. Patent No. 2,985,648, it is my view that issues of fraud in the procurement of the patent and of patent misuse raised by respondent and the Department of Justice, one or both of which issues may be relevant to section 337 patent-based proceedings, 1/ have not been explored sufficiently by the Commission to warrant a conclusion that a prima facie showing of violation of section 337 has been established. It is therefore premature to recommend a temporary exclusion order at this time.

1/ The issue of fraud in the procurement of a patent has not previously been raised under section 337, but patent misuse has been raised. Former Commissioner Thunberg, the late Commissioner Newsom and I held that patent misuse is relevant to proceedings of the Commission under section 337; Furazolidone, Inv. No. 337-21, T.C. Publication 299, November 1969.

Statement of Commissioner Leonard

The facts obtained in the preliminary inquiry establish good and sufficient reason for the ordering of a full investigation but do not warrant a recommendation for the issuance of a temporary exclusion order to forbid entry into the United States of ampicillin and any products containing ampicillin.

The standard adopted by the Commission for determining whether a temporary exclusion order should be recommended (as indicated to the parties by letter notice) is: "whether complainant has made a prima facie showing of violation of section 337 and whether, in the absence of a temporary order of exclusion, immediate and substantial harm would be sustained."

Commissioner Sutton distinguished the standard for recommending a temporary exclusion order from the standard for recommending a permanent exclusion order in the Furazolidone case: "This standard of 'immediate and substantial harm,' which interested parties were notified would be the basis for the Commission's determination with respect to a temporary exclusion order, is more strict than that set forth in the section 337 statutory language, which requires merely that 'the. . .tendency' of the unfair acts be such as to 'substantially injure an industry'. The 'immediacy' of the substantial harm being the essential difference between the two standards. . . ." 1/

1/ Furazolidone, (Preliminary Investigation No. 337-21, August, 1968).

The facts obtained in the preliminary inquiry do not reveal at this time the immediacy of substantial harm necessary for recommending a temporary exclusion order. No evidence has been obtained indicating that the domestic industry has undergone any reduction in sales, idling of production facilities, or decrease in profitability, nor is there any evidence that it is likely to in the near future. On the contrary, production of ampicillin increased from an estimated 120,000 kilograms in 1967 to 312,000 kilograms in 1969, and during this time production increased at an average annual rate of 61 percent. Although current figures seem to indicate that imports of ampicillin are increasing, information obtained in the preliminary inquiry indicates that in 1969 the ratio of imports to domestic production was small, or, in other words, that imports represent an insignificant share of the domestic market.

During the time the Commission's full investigation is being conducted, either the complainants or the respondent must bear the burden of the lost sales, or in the case of complainant Beecham Group Limited the lost royalties, depending upon whether or not a temporary exclusion order is issued. To assess the burden properly, it must be determined whether the interests of the patent holder (complainant Beecham Group Limited), its American subsidiary (Beecham, Inc.), and its licensees outweigh that of the importer (the respondent), or whether the reverse is true. In addition, there is a third interest to be considered here, namely, that of the public.

The respondent, Zenith Laboratories, Inc., is the only domestic importer of ampicillin, and, as a generic manufacturer, its prices to the wholesale trade are substantially lower than those of the domestic manufacturers. This savings in price is passed on to the ultimate consumer. The public interest in having a life-saving drug available at a considerably lower price must be added to the interest of respondent and balanced against the interest of the complainants. The evidence of immediate and substantial harm to the complainants must be strong and convincing to overcome the interests of the consuming public and the respondent. Such strong and convincing evidence of substantial harm to the complainants has not yet been produced.

In addition, I concur with the view expressed by Presiding Commissioner Sutton that the recommendation of a temporary exclusion order is premature at this time because the issues of fraud in the procurement of the patent and of patent misuse, raised by the respondent and the Department of Justice, and which may be relevant to 337 proceedings, have not been explored sufficiently to determine whether a prima facie showing of violation of the statute has been established.

The full investigation should move forward quickly so that a decision on the merits and a recommendation to the President, if justified, can be made forthwith. Since the Commission can recommend to the President a temporary exclusion order at any time during the course of a full investigation, if the immediacy of the harm to the complainants is revealed subsequently, the Commission should at that point recommend the order. But, for now, no such recommendation should be made.

Description and Uses

Ampicillin is the USAN (United States Adopted Name) or accepted nonproprietary name for 6-(D-2-amino-2-phenylacetamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, also known as (D-α-aminobenzyl)penicillin. It is included in the United States Pharmacopeia, Eighteenth Revision.

Ampicillin is the most widely used of the semi-synthetic penicillins--a group of penicillins which was developed, largely through the research efforts of Beecham Group, Limited, in an effort to produce a penicillin product lacking the deficiencies of penicillin G and the other available penicillins produced by direct fermentation. These deficiencies are summarized as follows:

1. Penicillin G is split by acids and is therefore inactivated by gastric juices; it is consequently most effective when given by injection, although it can be effective orally provided it is given to a fasting patient in buffered doses.

2. It is split by the enzyme penicillinase, which is produced by many species of micro-organisms, and consequently is ineffective against any such organism.

3. It is generally ineffective against gram-negative organisms.

4. It produces allergic reactions in many patients.

5. Some pathogenic species which are susceptible to penicillin G have developed penicillin-resistant strains.

Although it is slightly less active against gram-positive organisms than penicillin G, ampicillin is effective against a broader spectrum of gram-negative organisms than either penicillin G or the other semi-synthetics, and it is more resistant to acids than penicillin G. Except for occasional allergic reactions, all the penicillins, including ampicillin, are free from the serious and sometimes fatal side effects of the broad-spectrum antibiotics. Ampicillin has the additional advantage of being less bound to serum than either the other penicillins or the broad-spectrum antibiotics, so that it is comparatively more effective at any given blood level. Unlike most of the other semi-synthetic penicillins, however, it is inactivated by penicillinase and is therefore useless against penicillinase-producing organisms. In summary, ampicillin has a broader antibacterial spectrum than any of the other penicillins and lacks the serious side effects of the broad-spectrum antibiotics. It is widely prescribed throughout the world for the treatment of gastrointestinal, respiratory, and urinary tract infections caused by certain non-penicillinase-producing gram-negative organisms and is particularly valuable against some forms of meningitis. It was recently termed one of the fifteen outstanding medical developments of the past ten years by a group of expert consultants polled by a private medical newsletter.

The penicillins are a group of antibiotics produced wholly or partially by a fermentation process using various species of the penicillium mold; chemically, they are all derivatives of 6-amino-penicillanic acid (hereafter referred to as 6-APA). Penicillin G

(or benzylpenicillin) was the principal ingredient of the original penicillin mixture produced by the natural fermentation process and still remains the most widely used of all the penicillins. In order to increase the yield of penicillin G and eliminate unwanted side products, the standard commercial practice is to add a suitable precursor chemical such as phenylacetic acid to the fermentation broth. Penicillin V (or phenoxymethylpenicillin) and penicillin O (allylmercaptomethylpenicillin) are likewise produced by adding appropriate precursors to the broth.

By contrast, ampicillin and the other semi-synthetics are made by acylating 6-APA, obtained either by direct fermentation or by enzymatic cleavage of penicillin G, with a suitable organic acid. Thus acylation with D-(-)-α-aminophenylacetic acid yields ampicillin, while acylation with 2,6-dimethoxybenzoic acid and with α-phenoxypropionic acid yields methicillin and phenethicillin, respectively. Many other semi-synthetic penicillins have been made for experimental purposes; eight of them (including the three mentioned above) were produced commercially in the United States in 1968.

Ampicillin is used, as anhydrous ampicillin or as ampicillin trihydrate, 1/ in the form of 250 and 500 mg. capsules, chewable tablets, oral suspensions, and pediatric drops; it is also used in injectible form as the water-soluble sodium salt.

1/ Bristol-Myers Company holds the patent on ampicillin trihydrate.

U.S. Producers

U.S. producers of ampicillin are Beecham, Inc. (U.S. operation of Beecham Group, Ltd., of England); the Beecham licensees, Bristol Laboratories, Inc., and the Bristol-Myers Company; and the Bristol sub-licensees, Squibb-Beechnut, Inc. (Squibb Division), and the American Home Products Corp. (Wyeth Division). In addition, there are distributors purchasing ampicillin in dosage form from Bristol (Parke, Davis & Co.) and from Beecham (Ayerst Laboratories Division of American Home Products Corp. and Lederle Laboratories Division of American Cyanamid Company).

Beecham, Inc.

Beecham, Inc., was incorporated in the State of New Jersey, on August 31, 1967. It is a subsidiary of Beecham Group Ltd., of England, which owns approximately 90 percent of the outstanding common stock of the New Jersey corporation.

Beecham, Inc., is engaged in the manufacture of prescription and proprietary drugs, and toiletries. Its leading products are ampicillin and other broad spectrum semi-synthetic penicillins, "Eno" antacid, "Macleans" toothpaste, and "Brylcreem" hair dressing for men. These products are sold in the United States, Canada, Latin America, Australia, and New Zealand.

The company's main office and plant are located in Clifton, New Jersey. A new $6 million pharmaceutical plant, engaged in the manufacture of semi-synthetic penicillins and in process and product development research, was completed in March 1970 in Piscataway, New

Jersey. It also owns plants of subsidiaries in Canada, Venezuela, Brazil, Argentina, Mexico, Australia, and New Zealand.

During 1970, Beecham further consolidated its pharmaceutical operations in the United States. It acquired the minority interest in Beecham Research Laboratories, Inc., formerly a 51 percent-owned subsidiary. It signed distribution agreements with Ayerst and Lederle, as a result of which, the marketing of Beecham's semisynthetic penicillins in the United States was expanded. Total employment by the company stood at 1,826 on March 31, 1970, a 60-percent increase over the level of March 31, 1967.

For the fiscal year ended March 31, 1970, Beecham, Inc., had net sales of nearly $82 million, compared with nearly $77 million for the fiscal year ended March 31, 1969. Net income for the corporation was in excess of $13 million in fiscal 1970, compared with more than $12 million in fiscal 1969. Capital expenditures totaled $7.2 million in fiscal 1970, approximately the same amount so expended during the preceding three fiscal years, combined; in fiscal 1969, this expense was less than $1.6 million.

Bristol-Myers Company

Bristol-Myers Company was originally incorporated in New York on June 9, 1900, as the successor to the Clinton Pharmaceutical Company founded in 1887. On August 11, 1933, Bristol-Myers was incorporated in the State of Delaware. On September 1, 1933, the company acquired all the capital stock of Bristol-Myers Company of New Jersey from Drug, Inc., upon dissolution of the latter corporation.

Bristol-Myers functions as both an operating and a holding company. As of December 31, 1968, it controlled 100 percent of the voting stock of Bristol-Myers International Corp.; Luzier, Inc.; Westwood Pharmaceuticals, Inc.; Mead Johnson and Company (and Mead Johnson Canada, Ltd.); the Lenk Co.; Sybil Ives, Inc.; the Drackett Co.; Clairol, Inc.; Biochemical Procedures, Inc.; Bristol-Myers Canada, Ltd.; and Bristol Laboratories of Canada, Ltd. Principal U.S. plants are situated in East Syracuse, N.Y.; Hillside, N.J.; Stamford, Conn.; Urbana and Cincinnati, Ohio; Chicago, Ill.; Ladue, Mo.; Evansville, Ind.; and Zeeland, Mich. The company also has plants in the following countries: Canada, Mexico, Brazil, Argentina, the United Kingdom, West Germany, Austria, South Africa, and Australia.

Bristol-Myers and its affiliated companies are engaged in the manufacture of prescription and proprietary drugs, toiletries and cosmetics, nutritional products, and household products of varied types. At the close of 1969, total Bristol employees exceeded 26,000.

Bristol Laboratories produce synthetic and semi-synthetic penicillins, including "Polycillin," their trademark for ampicillin; "Tetrex," a tetracycline; other antibiotics; an anti-hypertensive; and a nasal decongestant. During 1969, Bristol Laboratories completed a new laboratory wing and clinical chemical building in Syracuse, N.Y., and began construction of a new plant in Barceloneta, Puerto Rico. About 16 percent of the 3,000 employees of Bristol Laboratories are engaged in research and development work.

For the calendar year 1969, Bristol-Myers had net sales of $928 million, compared with $850 million in 1968 and $304 million in 1960. Net earnings in 1969 amounted to almost $68 million, compared with $59 million in 1968 and $25 million in 1960.

Bristol-Myers spent $34 million on research in 1969, a record high which was more than double the amount spent in 1964. The company received royalty payments in excess of $6 million in 1969. It was estimated in 1968 that the annual rate of profit for Bristol was about 14 percent of net sales.

American Home Products Corporation

The American Home Products Corporation was incorporated in Delaware on February 4, 1926, as a consolidation of several manufacturers of proprietary drug products. The corporation functions as both an operating and management enterprise.

The corporation with its subsidiaries produces a great variety of pharmaceuticals, biologicals, nutritionals, animal health products, packaged drugs, toiletries, foodstuffs, candy, and a number of chemical specialties such as waxes, polishes, cleaners, and insecticides. With the merger of Ekco Products Company in September 1965, the corporation further diversified operations to include manufacturers of housewares, builders' hardware, bakers' equipment, and rigid aluminum foil containers.

Activities of the corporation are conducted through several divisions. Pertinent to this inquiry is the Prescription Drug Division,

which includes the laboratories of Wyeth, Ayerst, Ives, and Fort Dodge. These laboratories produce medicinal, pharmaceutical, biological, nutritional, and vitamin preparations, sold primarily through professional channels and advertised to the public.

The executive offices of the American Home Products Corporation are located in New York City. More than 50 plants, manufacturing laboratories, research centers, and warehouses are situated throughout the United States. Another 50 are located in foreign countries, especially those of Europe and Latin America.

Leading subsidiaries are the laboratories of the Prescription Drug Division (Wyeth, Ayerst, Ives, and Fort Dodge); the Whitehall and Franklin Laboratories, and the John F. Murray Advertising Agency, of the Packaged Drug Division; American Home Foods, Inc., of the Food Division; E. J. Brach and Sons, Inc., of the Candy Division; Ekco Products, Inc., of the Housewares Division; and the Prestige Group, Ltd., Boyle-Midway, Inc., and Dupli-Color, Canada, Ltd., of the Household Products Division. Other subsidiaries include the O. M. Franklin Serum Co. (U.S. & Canada), International Chemical Co., Ltd. (England), American Ethicals, Ltd. (South Africa), Adams Plastic Company (U.S.), A. R. Lite Manufacturing Company, Ltd., (Canada), Lucks, Inc. (U.S.), Elliot Marion Company, Ltd. (Canada), and the Household Research Institute (U.S.),

In 1969, prescription (ethical) drugs accounted for 36 percent of gross sales (about $460 million) of the Company and packaged drugs 17 percent (about $215 million). In foreign markets, these percentages

were 51 and 16, respectively.

Capital expenditures by the corporation for buildings and equipment totaled $33 million in 1969. This represented new manufacturing and research facilities for the Prescription Drug Division and a plant addition for the Candy Division. Construction of foreign facilities was expanded in Brazil, the United Kingdom, France, Germany, and Italy.

In 1969, net sales of the American Home Products Corp. rose to almost $1.2 billion, compared with nearly $1.1 billion in 1968. Net income also rose slightly in 1969 to $123 million, compared with $112 million in 1968 and less than $49 million in 1960.

By the end of 1969, the number of employees of the corporation totaled 40,427. The total on December 31, 1968, was 38,405; on December 31, 1960, total employment was 18,679.

Wyeth Laboratories.--Wyeth, the largest company in the Prescription Drug Division, with a broad line of pharmaceutical, biological, and nutritional products, shared in the steady increase of sales of the parent corporation, through 1969. The principal ethical drugs produced by Wyeth are "Omnipen," their trademark for ampicillin, "Tubex" injectible medications, "Ovral," an oral contraceptive, and "Serax," a mid-range tranquilizer.

The administrative and research center of the company is located in Radnor, Pa. Wyeth manufacturing laboratories are situated in Great Valley, Marietta, and West Chester, Pa.; Mason and Lake Odessa, Mich.; Chicago, Ill.; Appleton, Wisconsin; and Meridian, Idaho.

Wyeth International, Ltd., was operating in 126 foreign countries at the close of 1969. In addition to the products mentioned, this company has been making substantial sales in the overseas markets of infant formulas and the injectable forms of "Bicillin," a long-acting antibiotic used in the treatment of upper respiratory ailments, venereal diseases, and rheumatic fever. In 1969, the company continued to supply millions of doses of "Dryvax," a smallpox vaccine for the drive by the various U.S. and world health organizations to eradicate smallpox in West Africa. Large quantities of cholera vaccine were shipped to Korea to combat an outbreak of that disease.

During 1969, Wyeth scored several notable advances in research and development in the therapeutic field. Intensive clinical trials were begun with new compounds in the area of antibiotic and cardiovascular research, including a new, improved semi-synthetic penicillin.

Ayerst Laboratories.--Ayerst Laboratories is a manufacturer of ethical drugs, especially hormones and anesthetic, anti-infective and metabolic regulating agents. Manufacturing and research laboratories are located at Chazy and Rouses Point, New York.

In 1969, Ayerst continued in a pattern of consistent growth. In the U.S. market, leading Ayerst products were "Premarin," a drug in the field of estrogen replacement; "Atromid-S," in the cardiovascular field; vitamins; an anti-fungal preparation, "Grisactin-500"; and "Riopan Suspension," for relief of gastric hyperacidity. In Canada, sales were at a high level for "Premarin"; "Fluothane" an inhalation anesthetic; and two broad-spectrum penicillins, "Atromid-S" and

"Penbritin" (the Ayerst trademark for ampicillin).

Ayerst International, operating in twelve foreign countries (excluding Canada), also expanded plant facilities and increased sales during 1969. An Italian manufacturing plant was completed and became operative in July of that year. Additional sales outlets were projected for Europe and the Far East.

A new research unit for Ayerst was scheduled for operation in 1970, located at Chazy, in northern New York State. The unit will be equipped with the latest facilities available for evaluating all new drugs developed by Ayerst research for human use, with emphasis on compliance with Government safety standards.

Squibb, Beech-Nut, Inc.

The company was incorporated in Delaware, on August 24, 1967, as Squibb, Inc. Squibb, Beech-Nut, Inc., was formed as the result of the consolidation on January 15, 1968, of E. R. Squibb and Sons, Inc. (formerly a wholly-owned subsidiary of the Olin Mathieson Chemical Corporation) and Beech-Nut Life Savers, Inc. It is a diversified drug company, producing consumer brands in the fields of ethical and proprietary drugs, beverages, confections, specialty foods, and household products. In recent years, ethical pharmaceuticals, diagnostics, and medicinal chemicals have accounted for about 40 percent of the sales of the company.

Pharmaceuticals are manufactured by the wholly-owned E. R. Squibb and Sons, Inc., for sale to pharmacies and the medical profession. These products include drugs for the treatment of infectious diseases,

cardiovascular disorders, mental diseases, and cancer; diagnostic agents; and preparations for the treatment of nutritional deficiencies. The company is a leading U.S. producer of antibiotics, corticosteroids, sex hormones, antihypertensives, contrast agents, vitamins, and radioactive pharmaceuticals. Most of these products are also manufactured in foreign countries by subsidiaries and licensees.

Leading Squibb antibiotics in the U.S. market are "Principen" (their trademark for ampicillin), "Pentids," and "Sumycin." The popular "Theragran" line of high potency vitamin preparations registered a record high for U.S. sales in 1969.

E. R. Squibb and Sons, Inc., owns a new (1969) plant and laboratory in New Bruswick, New Jersey. It leases branch warehouses in 12 major U.S. cities. Its foreign subsidiaries and affiliates have plants in Canada, Mexico, Colombia, Peru, Argentina, Brazil, Uruguay, England, Ireland, France (3), West Germany, Italy (2), Spain, Turkey, South Africa, Australia, the Philippines, and India (2). Licensee plants are located in Venezuela, Belgium, Sweden, Japan, Hong Kong, Pakistan, Taiwan, and Thailand.

Wholly-owned subsidiaries of Squibb, Beech-Nut, Inc., in addition to E. R. Squibb and Sons, Inc., are Beech-Nut, Inc.; Life Savers International Corporation; Life Savers Ltd., Canada; Millbrook, Inc.; Table Talk, Inc.; Tetley Tea Company, Ltd.; and Dobbs Houses, Inc. During 1969, the parent corporation acquired the J. B. Food Services, Inc., of Wrightson, N. J., and E. R. Squibb and Sons acquired Specific Serums, Inc.; Hoboken, N. J., a producer of blood diagnostic agents.

Squibb also acquired in 1969 two pharmaceutical operations in Greece and one in Canada.

During 1969, the net sales of Squibb, Beech-Nut, Inc., rose to about $645 million, compared with $615 million in 1968; of these sales totals, pharmaceuticals, proprietary drugs and household products, combined, accounted for $291 million in 1969 and $271 million in 1968. Net income of the parent corporation was almost $43 million in 1969, compared with $35 million in 1968. Inventories totaled nearly $114 million in 1969, compared with $94 million in 1968. A total of $24 million was spent on research development in 1969, nearly $23 million in 1968, and more than $20 million in 1967. Capital expenditures were more than $49 million in 1969, compared with some $27 million in 1968. A total of over 31,000 persons were employed by Squibb, Beech-Nut, Inc., as of December 31, 1969.

During 1969, Squibb completed construction of a new manufacturing plant and quality-control laboratory at New Brunswick, N. J.; the company expects to consolidate all of its U.S. pharmaceutical manufacturing at this location. The Squibb plant in Brooklyn, N. Y., was sold, and all employees offered employment in New Brunswick. The new plant is expected to give the company improved control over the quality of its pharmaceuticals, as well as increased efficiency and capacity in their manufacture.

Also in 1969, Squibb commenced construction of a new plant in Lawrence Township, N. J., which will contain research laboratories and executive offices. Another new Squibb pharmaceutical plant was

started in Regensburg, West Germany. Construction was also initiated on new facilities for the manufacture of bulk pharmaceuticals in both Puerto Rico and Italy. The company acquired all of the outstanding majority stock in the Squibb affiliate in Italy.

U.S. Production and Sales

The following tabulation, based principally on data reported to the U.S. Tariff Commission by the producers, shows U.S. production and sales (including export sales) of bulk ampicillin for the years 1967-1969. Data for 1967 include some estimates.

		Sales		
Year	Production 1,000 Kg.	Quantity 1,000 Kg.	Value $1,000	Unit value per gram
1967	E 120	E 32	E 10,767	E .34
1968	191	54	15,756	.29
1969	312	72	18,807	.26

E = estimated.

As shown in the tabulation, production of ampicillin increased from an estimated 120,000 kilograms in 1967 to 312,000 kilograms in 1969 an average annual increase of 61 percent. The difference between production and sales represents primarily the amounts used captively by the producers in the manufacture of finished pharmaceutical products.

According to the complaint filed by the Justice Department in its antitrust suit against Bristol and Beecham, world-wide sales of

semi-synthetic penicillins in dosage forms by these two companies and their licensees amounted to approximately $170 million in 1968. Half of this amount--or $85 million--was accounted for by U.S. sales, consisting mostly of ampicillin. Bristol's brand of ampicillin, Polycillin, had sales in 1968 of $52.2 million; Ayerst's Penbritin (purchased from Beecham) had sales of $14.0 million; Wyeth's Omnipen, $10.0 million; Parke, Davis' Amcill, (purchased from Bristol), $3.4 million; and Squibb's Principen, $3.3 million. Not yet on the market in 1968 were Beecham's brand, Totacillin, and Lederle's Alpen (purchased from Beecham). The value of U.S. sales of ampicillin in dosage forms in 1969 is estimated to have exceeded $120 million.

U.S. Importer
(Zenith Laboratories, Inc.)

Zenith Laboratories, Inc., was incorporated in the State of New Jersey in 1956. During 1967-70, it entered into a period of rapid growth and expansion. The new headquarters and modern manufacturing and technical facilities of the company are located in Northvale, New Jersey, with additional production facilities situated in Englewood, New Jersey, and in St. Croix in the Virgin Islands. Major distribution operations are centered at Northvale and at Philadelphia, Pa.

Zenith is a producer of generic ethical and proprietary drugs. Its total line of generic drugs increased in number to 145 by December 31, 1969, compared with 40 at the end of 1968. Such antibiotics as ampicillin and tetracycline are prominent items in the Zenith line. These generic drug products are sold throughout the United States, to such customers as wholesalers, drug chains, mail order houses, and government agencies.

In addition to the plants in New Jersey and the Virgin Island, Zenith acquired in 1969 two drug distribution subsidiaries, Paramount Surgical Supply Company, and Pace-Bond Company; both of these companies moved into new and expanded facilities during that year. Another subsidiary, Mexico Forge, a manufacturer of playground and recreation equipment, completed construction of a new plant in Reedsville, Pa., during 1969.

By 1970, all encapsulating by Zenith of ampicillin and other antibiotics was done in St. Croix, the Virgin Islands, at the plant

of another wholly-owned subsidiary, the Pralex Corporation. This subsidiary imports the bulk ampicillin from the Ankerfarm, S.p.A., of Italy. Pralex purchased, on November 20, 1968, the former plant of Continental Laboratories in St. Croix; previously, Pralex had produced other penicillin and sulfa products.

For the calendar year 1969, the net sales of Zenith, Inc., amounted to almost $7.5 million, compared with $3.4 million for 1968. Expenditures for property, plant and equipment totaled nearly $1.5 million in 1969, compared with $166,000 in 1968 and $40,000 in 1967, reflecting the recent expansion of company activities. Net earnings of Zenith in 1969 were $211,717, below the $311,358 of 1968 because of the heavy expenditures for plant expansion and losses incurred by Paramount and Mexico Forge; net earnings in 1969, however, exceeded those of 1967, which amounted to $116,258. During 1969, the total number of Zenith employees rose from 70 on January 1 to 325 on December 31.

The stock of Zenith, Inc., is widely held, traded over the counter. At the close of 1969, about 80 percent of the common stock was publicly held, and the remaining 20 percent was held by "insiders." About 6 to 8 percent of the total common stock was held in escrow, under the terms by which Zenith was purchasing tetracycline from Ankerfarm in exchange for stock.

U.S. Imports

Zenith Laboratories, Inc., of Northvale, N.J., is believed to be the sole importer of ampicillin. According to data furnished by Zenith's attorney, the company, in March 1969, made an initial importation direct from Italy into the United States of 250 mg. capsules of ampicillin trihydrate. Subsequent imports from Italy have consisted entirely of bulk ampicillin trihydrate, of which one shipment was imported directly into the United States and the remainder was imported into the Virgin Islands, where it was encapsulated by a wholly-owned subsidiary and then re-exported to Zenith in the United States. All of the imports have been supplied by Ankerfarm, S.p.A., a German firm which allegedly built a plant in Italy to take advantage of Italy's lack of patent protection for drugs.

Zenith's admitted imports of ampicillin in 1969 and in the first half of 1970 were equivalent to somewhat less than 5 percent of U.S. production. It appears that the total of imports in 1970 will be considerably larger than those entered in 1969. Zenith was just beginning to import ampicillin in 1969 and was in the process of establishing itself as a supplier of generic ampicillin. It has advertised ampicillin widely in periodicals directed at retail pharmacists and has recently introduced ampicillin in 500 mg. capsules and in bottles for oral suspension. It is believed that Zenith is now an important factor in the market for generic ampicillin, which is estimated at about 20 percent of the total ampicillin market of the United States.

Tariff Treatment

Ampicillin is classifiable under TSUS item 407.85, "other" benzenoid drugs, and is dutiable at a compound rate of 2.45¢ per pound plus 17 percent ad valorem (third stage of the Kennedy Round reductions, effective January 1, 1970). Under the "American selling price" valuation system applicable to benzenoid chemicals, ampicillin is valued for duty purposes at the usual wholesale price of the competitive domestic product. Thus the ad valorem part of the duty on imported ampicillin is based on the value of domestic ampicillin rather than on the value of the imports.

Although the Virgin Islands are a U.S. possession, they have their own tariffs and are not a part of the customs area of the United States. Under the terms of a Danish law enacted in 1914 and retained in force under the terms of the treaty by which the United States acquired the Virgin Islands from Denmark in 1917, ampicillin may be imported into the Virgin Islands at an ad valorem duty of 6 percent, based on the foreign value.

Since the middle of 1969, Zenith has been importing ampicillin capsules from its subsidiary in the Virgin Islands free of duty under the provisions of headnote 3(a) of the Tariff Schedules of the United States, which stipulates that products of the Virgin Islands may enter the United States free of duty, provided they "do not contain foreign materials to the value of more than 50 percent of their total value."

Thus, as long as Customs officials are satisfied that Zenith's ampicillin meets the requirements of headnote 3(a), Zenith is able to realize a considerable savings on customs duty (6 percent of the foreign value instead of 17 percent of the "American selling price") by doing its encapsulating in the Virgin Islands rather than on the mainland.

Prices

On the basis of incomplete information obtained from a variety of sources, both official and unofficial, it appears that prices of ampicillin in dosage form, as charged by the manufacturers and distributors, vary considerably. For example, the popular 100-bottle of 250 mg. capsules is purchased directly from the manufacturer or distributor by druggists at wholesale prices ranging from about $10 per bottle from Zenith to approximately $22 from Bristol-Myers. Prices for the generic product are, of course, lower than those for the trademark brands of the leading U.S. producers and distributors.

Prices to the trade, as charged by leading U.S. manufacturers and distributors of ampicillin, are indicated in the following

tabulation: 1/

Price per 100 capsules of 250 mgs.

Trademark or generic name	Company	Wholesale price in direct purchases from manufacturer or distributor
Polycillin------	Bristol-Myers	$21.84
Amcill----------	Parke, Davis	21.60
Omnipen---------	Wyeth Labs.	19.14
Penbritin-------	Ayerst Labs.	21.82 1/
Alpen-----------	Lederle Labs.	19.10
Totacillin------	Beecham	2/
Principen-------	E. R. Squibb and Sons	19.00
Ampicillin------	Paramount (a Zenith subsidiary)	12.95 3/
Ampicillin------	Zenith	10.00 4/

1/ Wholesale price suggested by manufacturer.
2/ Beecham wholesale price was comparable to those for other trademark brands.
3/ Paramount Catalog #77, Winter 1969-70.
4/ Approximate wholesale price (March 1970).

Beecham Pharmaceuticals grants a standard cash discount of 2 percent within 30 days, on sales of ampicillin to the wholesale trade. It is believed that similar terms prevail for such sales by the other domestic manufacturers and distributors.

Wholesale prices of leading U.S. producers and distributors of ampicillin, for sales to hospitals, clinics, and government agencies, are quoted on the basis of individual bids, taking into account the cost factors and competitive situation for each customer. Under the licensing arrangements, the distributors purchase ampicillin in dosage form from the manufacturers according to individual price formulas.

1/ From "Drug Topics," published by the Drug Topics Redbook for 1970, unless otherwise indicated.

Royalties

Beecham Research Laboratories, Ltd., licensed Bristol-Myers to manufacture and sell ampicillin in the United States, through an agreement with Bristol Laboratories, Inc., in 1959 and a supplemental agreement with Bristol-Myers Company in 1960. These agreements also permitted Bristol to license other drug companies to produce and sell ampicillin in the United States, under the Beecham patent No. 2,985,648. Accordingly, Bristol-Myers began manufacturing ampicillin in 1963, and subsequently sub-licensed for the same purpose Squibb-Beechnut, Inc., and American Home Products Corporation (Wyeth).

Two distributors purchase ampicillin in dosage form from Beecham, Lederle Laboratories of the American Cyanamid Company and Ayerst Laboratories of the American Home Products Corporation. Parke, Davis and Company makes such purchases from Bristol-Myers.

Beecham received a royalty payment equivalent to 5 percent of their net sales from Bristol-Myers and the distributor-companies. It is believed that Bristol collected royalties at the same rate from its sub-licensees and distributors. Because of the alleged infringement of the patent and accompanying production and U.S. sales of ampicillin by Zenith Laboratories, the rate for these royalty payments to Beecham from Bristol-Myers was, according to the terms of the licensing agreement, reduced by one-half, i.e., to 2-1/2 percent.

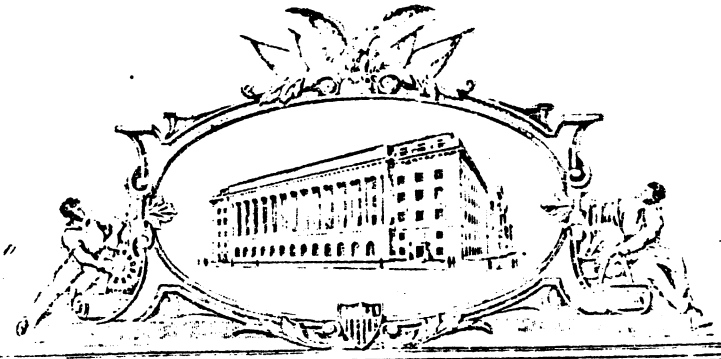
Such a "saving" on royalty payments is substantial in the case of Bristol-Myers, which accounted for approximately 60 percent of the total value of ampicillin sales in the United States during 1968.

Total sales of ampicillin in the U.S. market amounted to more than $80 million in 1968; total sales during 1969 were estimated to have been at least $120 million. Nevertheless, Bristol has joined Beecham in complaining against the alleged patent infringement and in associated litigation.

A P P E N D I X

Patent

APPENDIX



2,985,648

UNITED STATES PATENT OFFICE

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas Frank Peter Doyle, of Betchworth, England, John Herbert Charles Nayler and Harry Smith, both of Dorking, England,

PRESENTED TO THE **Commissioner of Patents** A PETITION PRAYING FOR THE GRANT OF LETTERS PATENT FOR AN ALLEGED NEW AND USEFUL INVENTION THE TITLE AND A DESCRIPTION OF WHICH ARE CONTAINED IN THE SPECIFICATION OF WHICH A COPY IS HEREUNTO ANNEXED AND MADE A PART HEREOF, AND COMPLIED WITH THE VARIOUS REQUIREMENTS OF LAW IN SUCH CASES MADE AND PROVIDED, AND

Whereas UPON DUE EXAMINATION MADE THE SAID CLAIMANT s are ADJUDGED TO BE JUSTLY ENTITLED TO A PATENT UNDER THE LAW.

NOW THEREFORE THESE **Letters Patent** ARE TO GRANT UNTO THE SAID

Frank Peter Doyle, John Herbert Charles Nayler, and Harry Smith, their heirs OR ASSIGNS

FOR THE TERM OF SEVENTEEN YEARS FROM THE DATE OF THIS GRANT

THE RIGHT TO EXCLUDE OTHERS FROM MAKING, USING OR SELLING THE SAID INVENTION THROUGHOUT THE UNITED STATES.

In testimony whereof I have hereunto set my hand and caused the seal of the Patent Office to be affixed at the City of Washington this twenty-third day of May, in the year of our Lord one thousand nine hundred and sixty-one, and of the Independence of the United States of America the one hundred and eighty-fifth.

[SEAL]

Ernest W. Swinder
Attesting Officer.

David L. Rine
Commissioner of Patents.

United States Patent Office 2,985,648 Patented May 23, 1961

2,985,648

ALPHA-AMINOBENZYLPENICILLINS

Frank Peter Doyle, 42 Hillside Gardens, Betchworth, England; John Herbert Charles Nayler, Coombelea, Cliftonville; and Harry Smith, Rockhouse, South Drive, Derpdene, both of Dorking, England

No Drawing. Filed Feb. 2, 1961, Ser. No. 81,630

Claims priority, application Great Britain Oct. 6, 1958

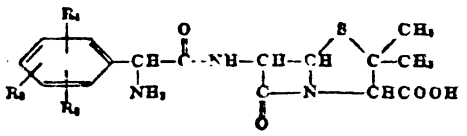
5 Claims. (Cl. 260—239.1)

This invention relates to new synthetic compounds of value as antibacterial agents, as nutritional supplements in animal feeds, as agents for the treatment of mastitis in cattle and as therapeutic agents in poultry and animals, including man, in the treatment especially of infectious diseases caused by Gram-positive and Gram-negative bacteria and, more particularly, relates to α-aminobenzylpenicillins and nontoxic salts thereof.

This application is a continuation-in-part of our prior co-pending applications Serial No. 844,162, filed October 5, 1959, and Serial No. 71,910, filed November 28,1960 both now abandoned.

Antibacterial agents such as benzylpenicillin have proved highly effective in the past in the therapy of infections due to Gram-positive bacteria but such agents suffer from the serious drawbacks of being unstable in aqueous acid, e.g., upon oral administration, and of being ineffective against numerous strains of bacteria, e.g., most Gram-negative bacteria. The compounds of the present invention are particularly useful in that they possess potent antibacterial activity against both Gram-positive and Gram-negative bacteria upon either parenteral or oral administration and also exhibit resistance to destruction by acid.

There is provided, according to the present invention, a member selected from the group consisting of an acid having the formula

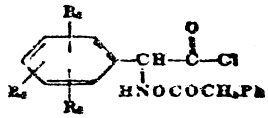


wherein R_1, R_2 and R_3 each represent a member selected from the group consisting of hydrogen, nitro, di(lower) alkylamino, (lower)alkanoylamino, (lower)alkanoyloxy, (lower)alkyl (including straight and branched chain saturated aliphatic groups having from 1 to 6 carbon atoms inclusive), (lower)alkoxy, sulfamyl, chloro, iodo, bromo, fluoro and trifluoromethyl; and the nontoxic carboxylic acid salts thereof, including nontoxic metallic salts such as sodium, potassium, calcium and aluminum, the ammonium salt and substituted ammonium salts, e.g., salts of such nontoxic amines as trialkylamines, including triethylamine, procaine, dibenzylamine, N - benzyl-beta-phenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, dehydroabietylamine, N,N'-bis - dehydroabietylethylenediamine, N-(lower)alkylpiperidine, e.g., N-ethylpiperidine and other amines which have been used to form salts with benzylpenicillin; and the nontoxic acid addition salts thereof (i.e., the amine salts) including the mineral acid addition salts such as the hydrochloride, hydrobromide, hydroiodide, sulfate, sulfamate and phosphate and the organic acid addition salts such as the maleate, acetate, citrate, oxalate, succinate, benzoate, tartrate, fumarate, malate, mandelate, ascorbate and the like. The α-carbon atom of the acyl group (to which the α-amino group is

attached) is an asymmetric carbon atom and the compounds of this invention can therefore exist in two optically active isomeric forms (the D-(—) and L-(+) diastereoisomers), as well as in the optically inactive DL form which is a mixture of the two optically active forms; all such isomeric forms of the compounds are included within the scope of the present invention. Also included within the scope of the present invention are easily hydrolyzed esters which are converted to the free acid form by chemical or enzymatic hydrolysis.

It should be noted in connection with the foregoing consideration of the diastereoisomers of this invention that many isomers other than the two caused by the asymmetric carbon of the side chain are possible due to the presence of asymmetric carbon atoms in the 6-aminopenicillanic acid nucleus. Such additional isomers, however, are not presently significant since 6-aminopenicillanic acid which is the product of fermentation processes is consistently of one configuration; such 6-aminopenicillanic acid is presently used in the production of the compounds of this invention.

The products of the present invention are prepared by reaction of 6-aminopenicillanic acid, preferably in the form of a neutral salt such as the sodium salt or the triethylamine salt, with an acid chloride having the formula



wherein R_1, R_2 and R_3 have the meanings given above, or its functional equivalent as an acylating agent for a primary amino group and thereafter removing the protecting group from the amino radical by hydrogenation under sufficiently mild conditions to avoid destruction of the penicillin nucleus. The protecting group,

$$PhCH_2OCO—$$

in the formula above may, of course, be replaced by another functionally equivalent protecting group as set forth below. The functional equivalents of the acid chloride set forth above include the corresponding carboxylic acid bromides, acid anhydrides and mixed anhydrides with other carboxylic acids, including monoesters, and particularly lower aliphatic esters, of carbonic acid.

The protected amino acid is preferably prepared by the method described in Example 1 below, which method is also discussed in "A Textbook of Biochemistry" by P. H. Mitchell, at page 113. In the next step, the 6-aminopenicillanic acid may be reacted with a mixed anhydride prepared by reacting the amino-substituted carboxylic acid, or a salt thereof, having its groups protected, with an ester of chlorocarbonic acid, e.g., ethyl chlorocarbonate. Alternatively, the protected amino-substituted carboxylic acid may be converted to a reactive acid halide.

The several methods used to form the aminoacyl derivatives of 6-aminopenicillanic acid (in which the amino group of the amino acid is protected) are standard procedures employed in peptide synthesis and include the use of a reactive acid azide or a carbodi-imide reagent cf. Sheehan and Hess, J. Amer. Chem. Soc., 1955, 77, 1067. The subsequent removal of the protecting group to form the free amino-substituted penicillin is effected by catalytic hydrogenation. Suitable protecting groups are of the general formula R"O.CO—, where R" is an allyl, benzyl (as shown in the formula above), substituted benzyl, phenyl or substituted phenyl group, or the trityl group Ph_3C—. The abbreviation "Ph" as used herein represents the phenyl group. The "carbobenzoxy" group

($PhCH_2OCO—$) is also sometimes referred to herein as the "carbobenzyloxy" group.

The diastereoisomers of the compounds of the present invention can be prepared by first preparing the appropriate amino acid having its amino group protected, e.g., DL-α-(carbobenzoxyamino)phenylacetic acid (the optically inactive racemic mixture of the optically active forms), and then separating the optically active forms of such acid, e.g., by way of their salts with optically active bases such as quinine, brucine, etc. and employing the appropriate form in the acylation of 6-aminopenicillanic acid. Thus DL-α-(carbobenzoxyamino)phenylacetic acid may be resolved to obtain D-(−)-α-(carbobenzoxyamino)phenylacetic acid and L-(+)-α-(carbobenzoxyamino)phenlacetic acid, each of which may be reacted with 6-aminopenicillanic acid as illustrated in Examples 7 and 8 to produce D-(−)-α-aminobenzylpenicillin and L-(+)-α-aminobenzylpenicillin, respectively.

The racemic mixtures of the amino acids, i.e., α-aminophenylacetic acid, α-amino-p-chlorophenylacetic acid and α-amino-p-methoxyphenylacetic acid, can be resolved according to methods which are described in detail in the technical literature, particularly in the following references: Betti and Mayer, Ber., 41, 2073 (1908); Ingersoll and Adams, J. Am. Chem. Soc., 47, 1168, (1925); Reihlen and Knopfle, Ann., 523, 199 (1936); Reihlen, Knopfle and Snopper, Ann., 534, 247 (1938); and Kuna, Ovakimian and Levene, J. Biol. Chem. 137, 334 (1941). The amino group of each of the two isomers of any of the amino acids so separated can then be protected by conversion to its carbobenzoxy derivative, and each such derivative can be used as described herein to acylate 6-aminopenicillanic acid and thus, after hydrogenation, produce the optically pure forms of the penicillins.

D-(−)-α-aminobenzylpenicillin has been found to be more soluble in water at its isoelectric point (about pH 4.7) and to be more active against several kinds of bacteria in vitro than is its isomer, L-(+)-α-aminobenzylpenicillin.

The Minimum Inhibitory Concentration (M.I.C.) in mcg./ml. in vitro against various strains of ten pathogenic Gram-negative organisms was determined by serial dilution in agar for both penicillin G, and α-D-(−)-aminobenzylpenicillin (referred to below as New Cpd.). The results were as follows:

Organism	M.I.C., mcg./ml.	
	New Cpd.	Penicillin G
E. coli	6.25	25.0
E. coli	12.5	50.0
Proteus vulgaris	6.25	25.0
Proteus vulgaris	3.5	6.25
Salm. typhi	0.8	2.5
Salm. typhi	0.8	2.5
Salm. typhi	0.6	2.5
Salm. typhi	0.8	0.6
Salm. typhimurium	2.5	6.25
Salm. paratyphi A	2.5	5.0
Salm. paratyphi B	2.5	6.25
Salm. paratyphi B	5.0	6.25
Shigella shigae	1.25	5.0
Shigella schmitzi	2.5	6.25
Shigella sonnei	6.25	50.0
Klebsiella pneumoniae	2.5	5.0

An elegant procedure for preparing a protected amino acid derivative of 6-aminopenicillanic acid by way of a mixed anhydride with ethoxy or isobutoxy-carbonic acid comprises mixing 0.01 mole of an acid having its amino group protected (whose acid chloride is set forth above), 0.01 mole isobutyl chloroformate and 0.011 mole tertiary hydrocarbonyl or aliphatic amine such as triethylamine or 2,6-dimethylpyridine (also known as 2,6-lutidine) in an anhydrous, inert, and preferably water-miscible solvent such as p-dioxane (e.g., 25 ml.) and if desired 2 ml. pure, dry acetone for about thirty minutes in the cold, e.g., at about 4° C. To this solution of the mixed anhydride there is then added a chilled solution of 0.01 mole 6-aminopenicillanic acid and 0.01 mole tertiary hydrocarbonyl amine, e.g., triethylamine or 2,6-dimethylpyridine, in, for example, 20 ml. of a solvent such as water. The reaction mixture is stirred for a period of an hour or so to form the substituted ammonium salt of the desired product. The mixture may then, if desired, be extracted at alkaline pH (such as pH 8; aqueous sodium bicarbonate may be used, for example, if necessary to adjust the pH) with a water-immiscible solvent such as ether to remove unreacted starting materials. The product in the aqueous phase is then converted to the free acid, preferably in the cold under a layer of ether by the addition of dilute mineral acid, e.g., 5 N H_2SO_4 to pH 2. The free acid is then extracted into a water-immiscible, neutral organic solvent such as ether and the extract is washed with water quickly in the cold, if desired, and then dried, as with anhydrous Na_2SO_4, and the carbobenzoxy groups protecting the amino groups are removed by hydrogenation. The product in its free form can then be converted to any desired metal, ammonium or substituted ammonium (i.e., amine) salt by treatment in an appropriate solvent with the appropriate base, e.g., a free amine such as procaine base or a solution of sodium or potassium 2-ethylhexanoate in dry n-butanol. The product can also be converted to any desired acid addition salt (of the amino group) by treatment of the product in an appropriate solvent with the appropriate acid, e.g., hydrochloric acid.

The removal of the protecting group is effected by allowing the protected aminoacyl derivative of 6-aminopenicillanic acid to react with hydrogen in the presence of a catalyst. This hydrogenation is normally carried out at room temperature and at atmospheric pressure, the pH of the reaction mixture being from 5 to 9. The solvent for the hydrogenation reaction is normally water, but other nonreducible solvents such as ethyl alcohol or dioxane or mixtures of these with water may be employed. The preferred hydrogenation catalyst is palladium but other catalysts such as platinum or rhodium may be used. The catalyst is preferably employed on an inert support, e.g., of barium carbonate, carbon, strontium carbonate or diatomaceous earth. Since the carbon atom next to that carrying the carbobenzyloxyamino group to be reduced is of an aromatic nature, the hydrogenation step is normally completed in a single treatment with hydrogen and catalyst.

Another method of preparing an ethereal solution of the acid form of the carbobenzoxy derivative of a compound of the present invention comprises preparing a solution in 20 ml. of water of 0.00463 mole 6-aminopenicillanic acid and 1.56 gm. sodium bicarbonate, adding 0.00475 mole of an acid chloride whose formula is set forth above and shaking vigorously at room temperature, e.g., for twenty to sixty minutes. The mixture is then extracted with ether to remove unreacted or hydrolyzed starting materials. The solution is then acidified (preferably in the cold) to pH 2, as with dilute sulfuric acid, and the free acid form of the product is extracted into ether (e.g., two portions of 25 ml.). This ethereal extract is dried, as with anhydrous sodium sulfate, and the drying agent is removed to leave a dry ethereal solution from which the product is easily isolated, preferably in the form of an ether-insoluble salt such as the potassium salt and the protecting groups are then removed from the amino groups by hydrogenation as described above. This procedure is used when the acid chloride reacts with a primary amine more rapidly than it does with water, as determined by simple test. In this procedure the acid chloride may be replaced by an equimolar amount of the corresponding acid bromide or acid anhydride. Since some of the antibiotic substances obtained by the process of this invention are relatively unstable compounds which readily undergo chemical changes resulting in the loss of an antibiotic activity, it is desirable to choose reaction conditions which are sufficiently mod-

erate to avoid their decomposition. The reaction conditions chosen will, of course, depend largely upon the reactivity of the chemical reagent being used. In most instances, a compromise has to be made between the use of very mild conditions for a lengthy period and the use of more vigorous conditions for a shorter time with the possibility of decomposing some of the antibiotic substance.

The temperature chosen for the process of preparation of the derivatives of penicillanic acid should in general not exceed 30° C. and in many cases a suitable temperature is ambient temperature. Since the use of strongly acid or alkaline conditions in the process of this invention should be avoided, it has been found preferable to perform the process at a pH of from 6 to 9, and this can conveniently be achieved by using a buffer, for example, a solution of sodium bicarbonate, or a sodium phosphate buffer. In addition to the use of aqueous media for the reaction, including filtered fermentation broths or aqueous solutions of crude 6-aminopenicillanic acid, use can be made of organic solvents which do not contain reactive hydrogen atoms. Examples of such inert solvents are dimethylformamide, dimethylacetamide, chloroform, acetone, methyl isobutyl ketone and dioxane. Frequently it is highly satisfactory to add an aqueous solution of a salt of 6-aminopenicillanic acid to a solution of the acylating agent in an inert solvent and preferably in an inert solvent which is miscible with water, such as acetone or dimethylformamide. Vigorous stirring is, of course, advisable when more than one phase is present, e.g., solid and liquid or two liquid phases. In the preparation of optically active isomers, mild conditions should be employed throughout the reaction in order to avoid racemization.

At the conclusion of the foregoing reaction, the products in which the amino groups are protected are isolated, if desired, by the techniques used with benzylpenicillin and phenoxymethylpenicillin. Thus the product can be extracted into diethyl ether or n-butanol at acid pH and then recovered by lyophilization or by conversion to a solvent-insoluble salt, as by neutralization with an n-butanol solution of potassium 2-ethylhexanoate, or the product can be precipitated from aqueous solution as a water-insoluble salt of an amine or recovered directly by lyophilization, preferably in the form of a sodium or potassium salt. When formed as the triethylamine salt, the product is converted to the free acid form and thence to other salts in the manner used with benzylpenicillin and other penicillins. Thus treatment of such a triethylamine compound in water with sodium hydroxide converts it to the sodium salt and the triethylamine may be removed by extraction, as with toluene. Treatment of the sodium salt with strong aqueous acid converts the compound to the acid form, which can be converted to other amine salts, e.g., procaine, by reaction with the amine base. Salts so formed are isolated by lyophilization or, if the product is insoluble, by filtration. A particularly elegant method of isolating the product as a crystalline potassium salt comprises extracting the product from an acidic, aqueous solution (e.g., pH 2) into diethyl ether, drying the ether and adding at least one equivalent of a solution of potassium 2-ethylhexanoate (e.g., 0.373 gm./mL) in dry n-butanol. The potassium salt forms, precipitates, usually in crystalline form, and is collected by filtration or decantation.

6-aminopenicillanic acid is prepared as set forth below or according to Batchelor et al., (Nature 183, 257–258, January 24, 1959) or Belgian Patent 569,728. It is used in the above reactions as the salt of a metal or a tertiary hydrocarbonyl amine or as an ester of a hydrocarbonyl alcohol. Hydrocarbonyl alcohols and tertiary hydrocarbonyl amines are compounds having the formulas

wherein the R groups contain only the elements carbon and hydrogen.

PREPARATION OF 6-AMINOPENICILLANIC ACID

The intermediate 6-aminopenicillanic acid is isolated after removal of the natural penicillins from penicillin fermentation broths prepared without the use of added precursors such as phenylacetic acid. For this purpose, suitable penicillin-producing moulds include species of Penicillium, for example, *Penicillium chrysogenum* 5120C, and the members of the notatum-chrysogenum group. The mould is grown preferably under aerobic submerged culture conditions. The culture medium used can be one of the generally accepted media commonly used in the preparation of penicillins. The culture medium usually consists essentially of a carbohydrate nutrient material, for example, glucose or lactose, calcium carbonate, sodium sulphate, and a nitrogenous material capable of providing the nitrogen necessary for the growth of the mould. The nitrogenous material can be either a natural substance, for example peanut meal, or it can be one or more chemical compounds containing nitrogen, for example, ammonium salts such as ammonium lactate or ammonium acetate. Where one or more chemical compounds are used as the nitrogenous material it is usual to incorporate in the culture medium very small amounts of a number of metals such as calcium, iron, zinc, copper, magnesium and manganese and these are normally introduced in the form of an aqueous solution of their salts. A suitable culture medium containing ammonium salts as the nitrogenous material is described by Jarvis and Johnson, J.A.C.S., 69, 3010, (1947), and J. Bact., 59, 51, (1950). Natural nitrogenous materials such as peanut meal usually contain sufficient amounts of suitable inorganic salts and thus when such materials are used in the culture medium it is usually not necessary to make a separate addition of inorganic salts.

The fermentation conditions used in the preparation of the fermentation liquor used in this invention can vary between wide limits, but it has been found preferable to use conditions similar to those commonly used in the preparation of Penicillin G. The temperature employed is preferably one from 20° C. to 35° C. and very satisfactory results have been obtained using a temperature of 25–27° C. The time required for the fermentation depends upon the culture medium and the mould used and the temperature at which the fermentation is carried out. Normal fermentation times are from 48 to 120 hours. The progress of the fermentation can be followed by means of periodic assay.

The fermentation liquor is obtained most satisfactorily when the fermentation is carried out under highly aerobic conditions. In the small scale operations referred to in the examples of this specification, aerobic conditions were achieved by shaking the fermentation mixture on a rotary shaking machine. When working on a larger scale, aerobic conditions can conveniently be obtained either by bubbling air or oxygen through the fermentation mixture, or by rapidly stirring the fermentation mixture. If desired, a combination of stirring and the bubbling of air or oxygen can be used.

It is sometimes preferred to prepare the antibiotic substances by the use of the isolated 6-aminopenicillanic acid or one of the intermediate concentrates obtained during its isolation. A concentrated solution of 6-aminopenicillanic acid can be prepared by evaporating the clarified harvest brew at reduced temperature and pressure to a small volume. If desired, the penicillins present in the brew can be largely removed by extraction with an organic solvent such as butyl acetate at an acid pH. After neutralizing the liquid substantial amounts of impurities can then be precipitated by the addition of solvents such as acetone, methanol or ethanol. After

separating such impurities the clear liquor may then be further concentrated to give a concentrated preparation.

The production by the process of this invention of antibiotic material from fermentation liquor having little or no antibiotic activity is clearly indicated if, before the addition of one of the chemical reagents hereinbefore specified to the fermentation liquor, the penicillins already present as a result of the fermentation reaction by which the fermentation liquor was obtained are removed. This removal can readily be achieved as indicated above by extracting the penicillins from the acidified fermentation liquor by means of an organic solvent, for example, butyl acetate, in which the penicillins are soluble.

This 6-aminopenicillanic acid was prepared and isolated as follows:

(*a*) A strain of *Penicillium chrysogenum* 5120C (obtained from Professor E. B. Chain, Istituto Superiore di Sanita, Rome) was first grown on a glycerol-molasses agar slope for 7 days at 26° C. Sterile distilled water was then added and the spores washed off the surface of the culture to produce a spore suspension. About 10 mls. of this suspension were used to inoculate 5 litres of seed medium in a 10-litre stainless steel stirred fermenter. The seed medium contained 8% w./v. corn steep liquor, 6% w./v. of dextrin and tap water, the pH being adjusted to 6.1 before sterilizing the fermenter and its contents. The tank was stirred at 500 r.p.m. with an air flow of 1 vol./vol./min. and maintained at 27° C. for 48 hours. A volume of 3.2 litres of the contents of this fermenter was then transferred aseptically into a 90-litre stainless steel fermenter containing 50 litres of fermentation medium consisting of peanut meal 3.0% w./v., lactose 4.0% w./v., Na_2SO_4 0.1% w./v., $CaCO_3$ 1.0% w./v. and tap water. The pH was adjusted to 7.2 before the fermenter and its contents were sterilized. After inoculation the tank was maintained at 26–28° C. for 4 days and stirred at 600 r.p.m. by means of an impeller of 12.5 cms. diameter. Air bubbled through the tank at the rate of 1 vol./vol./min. Foaming was controlled by the periodic addition of lard oil containing 2% of octadecanol.

The brew obtained was clarified and 40 litres thereof was concentrated in vacuo to a volume of 4 litres. The pH was then adjusted to 3.0 and the precipitate which formed was removed by centrifuging and the clear liquor was extracted once with half its volume of butyl acetate. The aqueous phase was separated and the pH adjusted to 7.5. Three volumes of acetone was then added with stirring and the precipitate removed by centrifuging. The clear liquor was then concentrated to 2280 mls. and the pH adjusted to 7.0. It had a potency of 54 u./mgm. assayed as described below.

The 6-aminopenicillanic acid was assayed by reacting a sample with phenylacetyl chloride and assaying the penicillin found by the cup plate method described by N. G. Heatley in Biochem. J. 38, 61 (1944) using *B. subtilis* as the bacterium. The purity of the preparation can then be expressed in units per mgm. (u./mgm.) of dry substance.

The potency of pure 6-aminopenicillanic acid assayed by this method is 2750 u./mgm.

(*b*) 1200 mls. of the concentrate of potency 54 u./mgm. were percolated through 200 gms. of Dowex 1 resin conditioned with hydrochloric acid. The column was washed with water and this wash was combined with the percolate. The assay of this solution proved it to contain 15% of the 6-aminopenicillanic acid applied. The column was then eluted with 0.05 N hydrochloric acid. The pooled active fractions of the eluate contained 81% of the original 6-aminopenicillanic acid, the solution assaying at 900 u./mgm. The eluate was then adjusted to pH 6.0 and concentrated to 25 mls. in vacuo, concentrated hydrochloric acid was added with stirring to bring the pH to 4.3 off and washed with water followed by acetone, and then dried in vacuo. The yield was 1.0 gm. assaying at 2200 u./mgm. (80% pure). Repeated precipitation of the crystalline material from neutral aqueous solution by the addition of hydrochloric acid gave a white crystalline solid of melting point 209–210° C. assaying at 2740 u./mgm. analyzing as follows: (Found: C, 44.6%; H, 5.7%; N, 13.1%; S, 14.1%. $C_8H_{13}O_3N_2S$ requires: C, 44.4%; H, 5.6%; N, 13.0%; S, 14.8%).

The following examples will serve to illustrate this invention without limiting it thereto.

Example 1

PREPARATION OF α-CARBOBENZOXYAMINOBENZYLPENICILLIN

α-Carbobenzyloxyaminophenylacetic acid (0.1 mole), which is obtained by the reaction of equivalent quantities of α-aminophenylacetic acid and benzyl chlorocarbonate in aqueous sodium hydroxide, dissolved in dry acetone is stirred and cooled to approximately −5° C. To this there is added dropwise with continued cooling and stirring a solution of ethyl chlorocarbonate (0.1 mole). After approximately ten minutes, the acylating mixture is cooled to about −5° C. and then is slowly added to a stirred ice-cold mixture of 6-aminopenicillanic acid (0.1 mole), 3% sodium bicarbonate solution (0.1 mole) and acetone. This reaction mixture is allowed to attain room temperature, stirred for an additional thirty minutes at this temperature and then is extracted with ether. The extracted aqueous solution is covered with butanol and the pH adjusted to 2 by the addition of N HCl. The acidified aqueous phase is extracted with butanol, the pH of the aqueous phase being adjusted to pH 2 each time. The combined butanol solutions which contain the free acid, α-carbobenzyloxyaminobenzylpenicillin, are washed with water, and are then shaken with water to which sufficient 3% sodium bicarbonate has been added to bring the aqueous phase to pH 7. This process of washing and shaking is repeated with fresh water and bicarbonate solution. The combined aqueous solutions are washed with ether and then are evaporated under reduced pressure and low temperature. The product, the sodium salt of α-carbobenzyloxyaminobenzylpenicillin, is obtained as a yellow solid in a yield of 65 percent.

Example 2

PREPARATION OF α-AMINOBENZYLPENICILLIN

A suspension of palladium on barium carbonate (3.7 grams of 30%) in water (20 ml.) is shaken in an atmosphere of hydrogen at room temperature. The catalyst is then filtered and washed well with water, care being taken that it does not become dry. A solution of the sodium salt of α-carbobenzyloxyaminobenzylpenicillin (6 grams) in water (20 ml.) is added to the pretreated catalyst and the suspension is shaken in an atmosphere of hydrogen at room temperature and pressure for one hour. The catalyst is then filtered off, washed well with water, and the combined filtrate and washings adjusted to pH 7 with N hydrochloric acid. The resulting solution is evaporated in vacuo at a temperature below 20° C. to give α-aminobenzylpenicillin (2.4 grams, 74% yield), which is assayed at approximately 48% pure by the manometric method. Paper chromatography shows that this material contains only one antibiotic which has a considerably different R_F value from that of the starting material.

The product, α-aminobenzylpenicillin [also known as 6-(α-aminophenylacetamido)penicillanic acid], contains the β-lactam structure as shown by infrared analysis, inhibits *Staph. aureus* at a concentration of 0.012 mcg./ml., and upon intra-muscular injection in mice, exhibits versus *Staph. aureus* Smith, *Salm. typhimurium* and *Strep. pyogenes* an ED_{50} of 0.05 mg./kg., 5.1 mg./kg. and 0.2 mg./kg., respectively. The product is very acid-stable,

under similar conditions the half-life (hours) of benzylpenicillin is less than 0.1.

Example 3

PREPARATION OF α-CARBOBENZYLOXYAMINO-P-CHLOROBENZYLPENICILLIN

α-Carbobenzyloxyamino-p-chlorophenylacetic acid (0.1 mole), which is obtained by the reaction of equivalent quantities of α-amino-p-chlorophenylacetic acid and benzyl chlorocarbonate in aqueous sodium hydroxide, dissolved in dry acetone is stirred and cooled to about −5° C. To this there is added dropwise with continued cooling and stirring a solution of ethyl chlorocarbonate (0.1 mole). After approximately ten minutes, the acylating mixture is cooled to about −5° C. and then is slowly added to a stirred ice-cold mixture of 6-aminopenicillanic acid (0.1 mole), 3% sodium bicarbonate (0.1 mole) and acetone. This reaction mixture is allowed to attain room temperature, stirred for an additional thirty minutes at this temperature and then is extracted with ether. The extracted aqueous solution is covered with butanol and the pH adjusted to 2 by the addition of N hydrochloric acid. The acidified aqueous phase is extracted with butanol, the pH of the aqueous phase being adjusted to 2 each time. The combined butanol solutions, which contain the free acid, α-carbobenzyloxyamino-p-chlorobenzylpenicillin, are washed with water to which sufficient 3% sodium bicarbonate to bring the aqueous phase to pH 7 has been added. This process of washing and shaking is repeated with fresh water and bicarbonate solution. The combined aqueous solutions are washed with ether and then are evaporated under reduced pressure and low temperature. The product, the sodium salt of α-carbobenzyloxyamino-p-chlorobenzylpenicillin is obtained as a yellow solid.

Example 4

PREPARATION OF α-AMINO-P-CHLOROBENZYLPENICILLIN

A suspension of palladium on barium carbonate (3.7 grams of 30%) in water (20 ml.) is shaken in an atmosphere of hydrogen at room temperature. The catalyst is then filtered and washed with water, care being taken that it does not become dry. A solution of the sodium salt of α-carbobenzyloxyamino-p-chlorobenzylpenicillin (4 grams, 42% pure) in water (20 ml.) is added to the pretreated catalyst and the suspension is shaken in an atmosphere of hydrogen at room temperature and pressure for one hour. The catalyst is then filtered off, washed well with water, and the combined filtrate and washings adjusted to pH 7 with N HCl. The resulting solution was evaporated in vacuo at a temperature below 20° C. to give α-amino-p-chlorobenzylpenicillin (88% yield, 45% pure by the manometric method). It was stable in acid solution and was shown to inhibit *Staph. aureus* at a concentration of 0.05 mcg./ml. The product may also be termed 6-(α-amino-p-chlorophenylacetamido)penicillanic acid.

Example 5

PREPARATION OF α-CARBOBENZYLOXYAMINO-P-METHOXYBENZYLPENICILLIN

α-Carbobenzyloxyamino-p-methoxyphenylacetic acid (0.1 mole), which is obtained by the reaction of equivalent quantities of α-amino-p-methoxyphenylacetic acid and benzyl chlorocarbonate in aqueous sodium hydroxide, dissolved in dry acetone is stirred and cooled to about −5° C. To this there is added dropwise with continued cooling and stirring a solution of ethyl chlorocarbonate (0.1 mole). After approximately ten minutes, the acylating mixture is cooled to about −5° C. and then is slowly added to a stirred ice-cold mixture of 6-aminopenicillanic acid (0.1 mole), 3% sodium bicarbonate (0.1 mole) and acetone. This reaction mixture is allowed to attain room temperature, stirred for an additional thirty minutes at this temperature and then is extracted with ether. The extracted aqueous solution is covered with butanol and the pH adjusted to 2 by the addition of N HCl. The acidified aqueous phase is extracted with butanol, the pH of the aqueous phase being adjusted to 2 each time. The combined butanol solutions, which contain the free acid, α-carbobenzyloxyamino-p-methoxybenzylpenicillin, are washed with water to which sufficient 3% sodium bicarbonate to bring the aqueous phase to pH 7 has been added. This process of washing and shaking is repeated with fresh water and bicarbonate solution. The combined aqueous solutions are washed with ether and then are evaporated under reduced pressure and low temperature. The product, the sodium salt of α-carbobenzyloxyamino-p-methoxybenzylpenicillin is obtained as a yellow solid.

Example 6

PREPARATION OF α-AMINO-P-METHOXYBENZYLPENICILLIN

A suspension of palladium on barium carbonate (3.7 grams of 30%) in water (20 ml.) is shaken in an atmosphere of hydrogen at room temperature. The catalyst is then filtered and washed with water, care being taken that it does not become dry. A solution of the sodium salt of α-carbobenzyloxyamino-p-methoxybenzylpenicillin (4 grams, 59% pure) is added to the pre-treated catalyst and the suspension is shaken in an atmosphere of hydrogen at room temperature and pressure for one hour. The catalyst is then filtered off, washed well with water, and the combined filtrate and washings adjusted to pH 7 with N HCl. The resulting solution was evaporated in vacuo at a temperature below 20° C. to give α-amino-p-methoxybenzylpenicillin (58% yield, 41% pure by the manometric method) which may also be termed 6-(α-amino-p-methoxyphenylacetamido)penicillanic acid. Paper chromatography showed only one antibiotic with a considerably different R_F value from the starting material. It was stable in acid solution and was shown to inhibit *Staph. aureus* at a concentration of 0.025 mcg./ml.

Example 7

PREPARATION OF 6-[D-(−)-α-AMINOPHENYLACETAMIDO]-PENICILLANIC ACID

D-(−)-α-(carbobenzyloxyamino)phenylacetic acid, M.P. 130–130.5° C., $[\alpha]_D^{21}$ −119.4° (C=3 in ethanol), is prepared by the action of benzyl chlorocarbonate on an ice-cold solution of D-(−)-α-aminophenylacetic acid in one equivalent of N aqueous sodium hydroxide, further sodium hydroxide being added as the reaction proceeds so as to keep the pH between 8 and 9.

Ethyl chlorocarbonate (4.8 ml.) is added to an ice-cold solution of the above carbobenzyloxy derivative (14.3 g.) and triethylamine (8.3 ml.) in dry acetone (420 ml.). The mixture is stirred at 0° C. for 5 minutes, during which triethylamine hydrochloride precipitates and the mixed anhydride is formed in solution. The suspension is cooled to −50° C. and stirred vigorously while adding as rapidly as possible an ice-cold solution of 6-aminopenicillanic acid (13 g.) in 3% aqueous sodium bicarbonate (420 ml.), the temperature of the mixture never being allowed to rise above 0° C. The resulting clear solution is stirred for 30 minutes at 0° C., then for a further 30 minutes while it attains room temperature, and finally extracted with ether (3×400 ml.), only the aqueous phase being retained. This aqueous solution is brought to pH 2 by the addition of hydrochloric acid and the 6-[D-(−)-α-(carbobenzyloxyamino) phenylacetamido]penicillanic acid so liberated is extracted into ether (150 ml. in 3 portions). Partial purification of this intermediate is effected by re-extracting it into aqueous sodium bicarbonate as the sodium salt and then, after re-adjusting to pH 2, back into ether as the free acid. Finally, it is re-converted to the sodium salt by shaking the ether solution with sufficient 3% sodium bicarbonate to give a neutral aqueous phase, separating the latter, and evaporating it at low temperature and pressure. The product is finally dried over phosphorus pentoxide in vacuo to give mod-

erately pure sodium 6-[D-(−)-α-(carbobenzyloxyamino) phenylacetamido]penicillanate (13 g.), which gives a single zone of antibiotic activity on a paper chromatogram.

A suspension of palladium on barium carbonate (38 g. of 30%) in water (125 ml.) is shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure for 1 hour. A neutral solution of sodium 6-[D-(−)-α-(carbobenzyloxyamino)phenylacetamido]penicillanate (20.4 g.) in water (250 ml.) is then added and shaking in hydrogen is resumed for a further 1 hour. The suspension is filtered and the combined filtrate and aqueous washings are treated with N-hydrochloric acid to pH 2, then washed with three 100 ml. portions of ether. The aqueous phase is adjusted to pH 4.65 by means of 3% sodium bicarbonate solution and then concentrated at low temperature and pressure to a volume of about 50 mL, whereupon fine colorless needles separate. After 30 minutes the crystals are collected, washed with a little cold water, and dried over phosphorus pentoxide in vacuo to give pure 6-[D-(−)-α-aminophenylacetamido]penicillanic acid monohydrate (5.5 g.), $[\alpha]_D^{21}+281°$ (C=1 in water), decomp. ca 202°. Recrystallization from water does not change the optical rotation. Analysis for $C_{16}H_{19}N_3O_4S.H_2O$: Found: C, 52.5%; H, 5.7%; N, 11.9%; S, 8.9%. Calculated: C, 52.3%; H, 5.8%; N, 11.4%; S, 8.7%.

A further 9 g. of less pure product is obtained by concentrating the aqueous filtrate. Like the first crop, it gives only a single zone of antibiotic activity on a paper chromatogram, which is different from that given by the unreduced carbobenzyloxy intermediate.

Example 8

PREPARATION OF 6-[L-(+)-α-AMINOPHENYLACETAMIDO]-PENICILLANIC ACID

L-(+)-α-(carbobenzyloxyamino)phenylacetic acid, M.P. 130–130.5° C., $[\alpha]_D^{21}+117°$ (C=3 in ethanol), is prepared from L-(+)-α-amino-phenylacetic acid by the method described for its enantimorph in Example 7 above. The product (14.3 g.) is converted into the mixed anhydride with ethyl chlorocarbonate as previously described and coupled with 6-aminopenicillanic acid (13 g.) to give 17.6 g. of moderately pure sodium 6-[L-(+)-α-(carbobenzyloxyamino)phenylacetamido]-penicillanate, which gives a single zone of antibiotic activity on a paper chromatogram.

Hydrogenation of this intermediate is carried out on the same scale and by the same method as that described in Example 7 above. The first crop of crystals (6.2 g.) consists of pure anhydrous 6-[L-(+)-α-aminophenylacetamido]penicillanic acid, $[\alpha]_D^{25}+209°$ (C=0.2 in water), decomp. ca, 205° C. Recrystallization from water does not change the optical rotation. (Found: C, 54.9%; H, 5.6%; N, 11.8%; S, 9.2%; $C_{16}H_{19}N_3O_4S$ requires C, 55.0%; H, 5.5%; N, 12.0%; S, 9.2%).

A further 6 g. of less pure product is obtained by concentrating the aqueous filtrate. Like the first crop, it gives only a single zone of antibiotic activity on a paper chromatogram, which is different from that given by the unreduced carbobenzyloxy intermediate.

Example 9

PREPARATION OF 6-[D-(−)-α-AMINOPHENYLACETAMIDO]-PENICILLANIC ACID (TRIETHYLAMINE PROCEDURE)

A total of 7.25 g. (0.0255 mole) of D-(−)-α-(carbobenzoxyamino)phenylacetic acid (M.P. 128–129° C.; $[\alpha]_D^{25}-116.5$ [C 1, alcohol]) and 4.25 ml. of triethylamine are dissolved in 210 ml. of acetone and stirred at 0° C. for 5 minutes. Two and four tenths milliliters (0.0255 mole) of ethyl chloroformate is added and the mixture is placed immediately in a Dry Ice-acetone bath at −50° C. A solution of 6.5 g. (0.030 mole) of 6-aminopenicillanic acid and 16 g. of sodium bicarbonate in 210 ml. of water is added all at once and the mixture is removed from the Dry Ice-acetone bath and stirred for ½ hour between −10° C. and 0° C. and finally for ½ hour at room temperature. The solution is diluted with 1 liter of ether and the aqueous layer which separates is removed. The pH is lowered with concentrated hydrochloric acid to 2 and the penicillin is extracted twice into 500 mL of ether; the ether is washed with water and finally with 75 ml. of saturated $NaHCO_3$. The aqueous bicarbonate solution is mixed with 8 grams of 5% palladium on strontium carbonate (Engelhard) and hydrogenated at 50 p.s.i. on a Parr low pressure hydrogenator for 1 hour. The catalyst is removed by filtration and the pH of the filtrate is lowered to 2 with concentrated hydrochloric acid and extracted with ether. The pH of the solution is adjusted to 4.65 with solid sodium bicarbonate and evaporated under reduced pressure (water pump) at 32° C. to a volume of 20 ml. A solid crystallizes which is filtered and found to weigh 2.85 g. One gram is recrystallized from 10 ml. of water by lowering the pH to 2 with a few drops of concentrated HCl and raising the pH to 4.65 with solid sodium bicarbonate to yield 0.25 g. of the pure product, 6-[D-(−)-α-aminophenylacetamido]penicillanic acid monohydrate, which is found to melt at 201° C. with decomposition. Anal. Calcd. for $C_{16}H_{19}N_3O_4S.H_2O$: N, 11.4%. Found: N, 11.14%; specific rotation: $[\alpha]_D^{25}+287°$ (C 0.1, water).

Example 10

PREPARATION OF 6-[D-(−)-α-AMINOPHENYLACETAMIDO]-PENICILLANIC ACID (LUTIDINE PROCEDURE)

To 5.5 g. (0.0193 mole) of D-(−)-α-(carbobenzoxyamino)phenylacetic acid and 2.6 g. of (0.0243 mole) 2,6-lutidine in 25 ml. of p-dioxane and 25 ml. of dry acetone at 0° C. is added 1.83 ml. (0.0193 mole) of ethyl chloroformate. A white precipitate forms and the mixture is stirred for 20 minutes. A solution of 4.95 g. of 6-aminopenicillanic acid in 50 ml. of water and 15 mL of 2,6-lutidine is added all at once. The clear solution is stirred for ½ hour and diluted with 500 ml. of ether. The aqueous layer is separated and solid $NaHCO_3$ is added to keep the pH at 8. The pH of the aqueous is lowered to 2 with concentrated hydrochloric acid and the penicillin is extracted into ether. The ether layer is washed with water and extracted with 25 ml. of saturated sodium bicarbonate solution. The sodium bicarbonate solution containing the penicillin is added to 10 g. of 5% palladium catalyst on diatomaceous earth (Engelhard) made to a paste by the addition of 15 ml of water. The penicillin is hydrogenated at 50 lbs. p.s.i. pressure on the Parr low pressure hydrogenator for 1 hour at room temperature. Because of the formation of a colloid the mixture is filtered through a Seitz filter. The pH is lowered to 2 by adding concentrated hydrochloric acid and extracted with ether to remove any of the starting penicillin. The aqueous layer is separated and the pH is adjusted to 4.65 by adding solid sodium bicarbonate. By evaporation under reduced pressure (water pump) at 32° C. the volume is reduced to 20 mL and the crystalline solid product, 6-[D-(−)-α-aminophenylacetamido]penicillanic acid monohydrate, is filtered off. Anal. calcd. for $C_{16}H_{19}N_3O_4S.H_2O$: N, 11.4%. Found: N, 11.34%.

Example 11

PREPARATION OF 6-[L-(+)-α-AMINOPHENYLACETAMIDO]-PENICILLANIC ACID

The procedure is the same as that described in Example 10 above using L-(+)-α-(carbobenzoxyamino)-phenylacetic acid $[\alpha]_D^{25}+85.5$ (C=1 in alcohol) in place of D-(−)-α-(carbobenzoxyamino)phenylacetic acid. Instead of 5% palladium on diatomaceous earth as in Example 10, 5% palladium on strontium carbonate is used. The product, 6-[L-(+)-α-aminophenylacetamido]penicillanic acid monohydrate, has the following

specific rotation and elemental analysis: $[\alpha]_D^{28}+20°$ (C=0.197 in water). Anal. Calcd. for

$C_{16}H_{19}N_3O_4S.H_2O$:

C, 52.3%; H, 5.7%; N, 11.4%. Found: C, 52.44%; H, 5.69%; H, 11.25%.

Example 12

When in the procedure of Example 1, the α-carbobenzyloxyaminophenylacetic acid is replaced by 0.1 mole of

α-carbobenzyloxyamino-4-diethylaminophenylacetic acid,
α-carbobenzyloxyamino - 4 - trifluoromethylphenylacetic acid,
α-carbobenzyloxyamino-2,4-dibromophenylacetic acid,
α-carbobenzyloxyamino-2-nitrophenylacetic acid,
α-carbobenzyloxyamino-3-methylphenylacetic acid,
α-carbobenzyloxyamino-4-sulfamylphenylacetic acid,
α-carbobenzyloxyamino-2-iodophenylacetic acid,
α-carbobenzyloxyamino-4-t-butylphenylacetic acid,

and

α-carbobenzyloxyamino-2-acetamidophenylacetic acid,

respectively, the following corresponding penicillin derivatives are produced:

α-carbobenzyloxyamino-4-diethylaminobenzylpenicillin,
α-carbobenzyloxyamino-4-trifluoromethylbenzylpenicillin,
α-carbobenzyloxyamino-2,4-dibromobenzylpenicillin,
α-carbobenzyloxyamino-2-nitrobenzylpenicillin,
α-carbobenzyloxyamino-3-methylbenzylpenicillin,
α-carbobenzyloxyamino-4-sulfamylbenzylpenicillin,
α-carbobenzyloxyamino-2-iodobenzylpenicillin,
α-carbobenzyloxyamino-4-t-butylbenzylpenicillin,

and

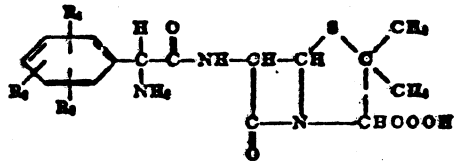
α-carbobenzyloxyamino-2-acetamidobenzylpenicillin.

Example 13

Replacement of the α-carbobenzyloxyaminobenzylpenicillin in the hydrogenation procedure of Example 7 by the following compounds, α-carbobenzyloxyamino-4-diethyl-aminobenzylpenicillin, α-carbobenzyloxyamino-4-trifluoromethyl-benzylpenicillin, α-carbobenzyloxyamino-2,4-dibromobenzylpenicillin, α-carbobenzyloxyamino-2-nitrobenzylpenicillin, α-carbobenzyloxyamino-3-methylbenzylpenicillin, α-carbobenzyloxyamino - 4 - sulfamylbenzylpenicillin, α-carbobenzyloxyamino-2-iodobenzylpenicillin, α-carbobenzyloxyamino - 4 - t - butylbenzylpenicillin, and α-carbobenzyloxyamino - 2 - acetamidobenzylpenicillin, respectively, results in the formation of the corresponding α-aminobenzylpenicillin, α-amino-4-diethylaminobenzylpenicillin, α - amino - 4 - trifluoromethylbenzylpenicillin, α-amino-2,4-dibromobenzylpenicillin, α-amino-2-nitrobenzylpenicillin, α - amino-3-methylbenzylpenicillin, α - amino-4-sulfamylbenzylpenicillin, α-amino-2-iodobenzylpenicillin, α - amino-4-t-butylbenzylpenicillin, α-amino-2-acetamidobenzylpenicillin, which are isolated as the free acid, and found to inhibit *Staph. aureus* at concentrations of 0.001 percent by weight.

We claim:

1. A member selected from the group consisting of the acids having the formula



wherein R_1, R_2 and R_3 each represents a member selected from the group consisting of hydrogen, nitro, di(lower)-alkylamino, (lower)alkanoylamino, (lower)alkanoyloxy, (lower)alkyl, (lower)alkoxy, sulphamyl, chloro, iodo, bromo, fluoro and trifluoromethyl and its sodium, potassium, calcium, aluminum and ammonium salts and its non-toxic substituted ammonium salts with an amine selected from the group consisting of tri(lower)alkylamines, procaine, dibenzylamine, N-benzyl-beta-phenethylamine, 1-ephenamine, N,N'-bis-dehydroabietylethylenediamine, N,N'-dibenzylethylenediamine and dehydroabietylamine.

2. α-Aminobenzylpenicillin.
3. α-Amino-p-chlorobenzylpenicillin.
4. α-Amino-p-methoxybenzylpenicillin.
5. D-(—)-α-aminobenzylpenicillin.

No references cited.