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⑦① Applicant: **ELI LILLY AND COMPANY**
307, East McCarty Street
Indianapolis Indiana 46206(US)

⑦② Inventor: Hall, David Alfred
2506, Bluffwood Drive
West Indianapolis Indiana 46208(US)

⑦④ Representative: Hudson, Christopher Mark et al,
Erl Wood Manor
Windlesham Surrey GU20, 6PH(GB)

⑤④ A process for electrolytic reduction of cephalosporin p-nitrobenzyl esters.

⑤⑦ A process is described for removing the p-nitrobenzylester protecting group from a cephalosporin 4-carboxylic acid pNB ester and thereby liberating the free cephalosporin 4-carboxylic acid; characterized in that the p-nitrobenzylester is electrolytically reduced in an acidic liquid medium comprising from about 0 to about 50% water, an acid having a pK_a determined in water of 0 or below, the amount of said acid being at least four moles per mole of the compound to be reduced, and an organic solvent substantially inert to electrolytic reduction, at the working electrode of an electrolytic cell, said working electrode substantially comprising carbon, mercury, tin, aluminium, silver, copper, lead, chromium, zinc, nickel or cadmium, at a temperature from about 0°C. to about 75°C., at a potential in a range from about the potential (A) of the initial onset of current flow of the first reduction to about the potential (B) of the initial onset of current flow of the second reduction.

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A PROCESS FOR ELECTROLYTIC REDUCTION OF
CEPHALOSPORIN p-NITROBENZYL ESTERS

This invention provides a superior method for the removal of the p-nitrobenzyl (hereinafter abbreviated to "pNB") ester group from cephalosporin carboxylic acids. The process is economically important, because cephalosporin antibiotics are often processed in the form of pNB esters, since the esters are convenient and economical to handle in chemical processing. The ester group must eventually be removed, however, because the cephalosporins are used as pharmaceuticals in the acid or salt form.

The pNB ester group has been used in the manufacture of cephalosporins for some time. See U.S. Patent 3,632,850, of Garbrecht. The pNB group has been removed chemically, such as with zinc and a strong acid, or catalytically, as taught by Garbrecht. Other deesterification methods have since been devised, such as the methods of Hatfield, using zinc and an α -hydroxy-carboxylic acid, U.S. Patent 4,091,214, or zinc and an organothiol, Belgian Patent 856,288, and the method of Jackson, U.S. Patent 3,799,924, using a dithionite salt.

All of the chemical and catalytic methods of deesterification, however, have the disadvantage that they may affect functional groups of the molecule other than the pNB ester.

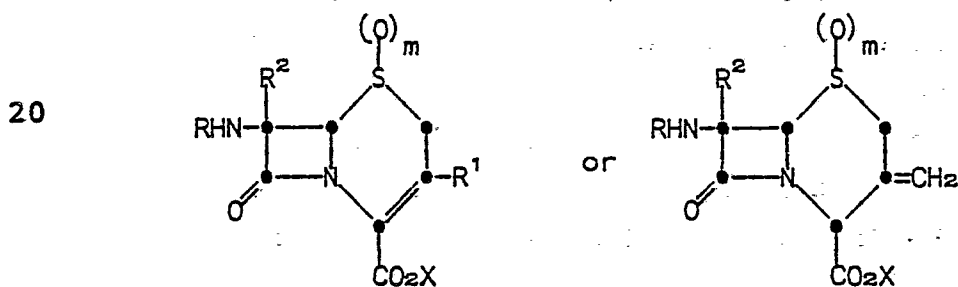
According to the present invention there is provided a process for removing the pNB ester protecting group from a cephalosporin 4-carboxylic acid pNB ester thereby liberating the free cephalosporin 4-carboxylic acid;

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characterized in that the pNB ester is electrolytically reduced in an acidic liquid medium comprising from about 0 to about 50% water, an acid having a pK_a determined in water of 0 or below, the amount of said acid being at least four moles per mole of the compound to be reduced, and an organic solvent substantially inert to electrolytic reduction, at the working electrode of an electrolytic cell, said working electrode substantially comprising carbon, mercury, tin, aluminum, silver, copper, lead, chromium, zinc, nickel or cadmium, at a temperature from about 0°C. to about 75°C., at a potential in a range from about the potential of the initial onset of current flow of the first reduction to about the potential of the initial onset of current flow of the second reduction.

Preferred compounds prepared by the process of the invention are those having the formula:

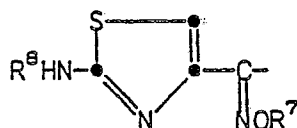


25 wherein X is hydrogen;
 m is 0 or 1;
 R^2 is hydrogen or methoxy;
 R is hydrogen or $-COR^3$;
 R^3 is hydrogen, C_1-C_3 alkyl, halomethyl,
 30 benzyloxy, 2,2,2-trichloroethoxy, t-butoxy,

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R^4 , $R^4-(O)_n-CH_2-$, $R^4-CH(R^5)-$, R^6-CH_2- , or



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wherein R^7 is hydrogen or C_1-C_3 alkyl and R^8 is hydrogen or an amino-protecting group;

R^4 is cyclohexadienyl or phenyl, or cyclohexadienyl or phenyl substituted with one or two halo, hydroxy, protected hydroxy, aminomethyl, protected amino-methyl, C_1-C_4 alkyl or C_1-C_4 alkoxy groups;

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n is 0 or 1;

R^5 is hydroxy, protected hydroxy, amino, protected amino, carboxy or protected carboxy;

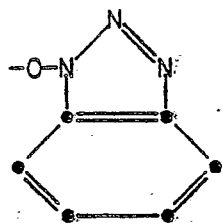
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R^6 is 2-thienyl, 2-furyl, 5-tetrazolyl or 1-tetrazolyl;

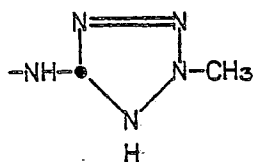
R^1 is chloro, C_1-C_3 alkyl or $-CH_2R^9$;

R^9 is C_1-C_4 alkanoyloxy, benzoyloxy, fluoro, chloro, carbamoyloxy, C_1-C_4 alkylcarbamoyloxy,

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pyridinio, pyridinio substituted with C_1-C_4 alkyl, C_1-C_4 alkanoyl, carbamoyl, C_1-C_4 alkyl-

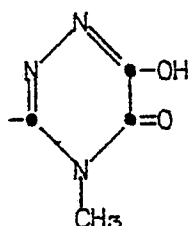
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carbamoyl, chloro, fluoro, hydroxy or trifluoromethyl, or the corresponding pyridinio chlorides or bromides, or $-S-R^{10}$;

R^{10} is $-CH_2CO_2(C_1-C_4 \text{ alkyl})$, carbamoyl, phenyl, phenyl substituted with one or two chloro, fluoro, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkylsulfonamido or tri-fluoromethyl groups;

triazol-3-yl unsubstituted or substituted with one or two groups independently selected from C_1-C_3 alkyl, $-CO_2(C_1-C_4 \text{ alkyl})$, $-CONH_2$ and $-CH_2NHOCO(\text{benzyl or } C_1-C_4 \text{ alkyl})$;



tetrazol-1-yl or tetrazol-5-yl substituted with one or two groups independently selected from C_1-C_4 alkyl and $-CH_2CO_2(C_1-C_4 \text{ alkyl or hydrogen})$; 4-cyano-5-aminopyrimidin-2-yl, or 5-methyl-1,3,4-thiadiazol-2-yl;

provided that n is 0 when R^4 is cyclohexadienyl.

In the above general formula, various generalized terms are used to describe the various groups. The generalized terms have their usual meanings in organic chemistry. For example, the term halomethyl includes bromomethyl, chloromethyl, fluoromethyl and iodomethyl.

The group R^3 is a 2-amino-4-thiazolyl(alkoxyimino)methyl group. The alkoxyimino group of this group may be in either the syn or anti form.

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The terms C_1-C_3 alkyl, C_1-C_4 alkyl and C_1-C_4 alkoxy include groups such as methyl, ethyl, propyl, butyl, s-butyl, t-butyl, methoxy, isopropoxy and i-butoxy.

5 The term protected amino refers to an amino group substituted with one of the commonly employed amino-protecting groups such as t-butoxycarbonyl, benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl and 1-carbomethoxy-2-propenyl.

10 Other accepted amino-protecting groups such as are described by J. W. Barton in Protective Groups in Organic Chemistry, J.F.W. McOmie, Editor, Plenum Press, New York, 1973, chapter 2 will be recognized by organic chemists as suitable for the purpose.

15 The term protected carboxy refers to an acid group protected with any group which is conventionally used to block or protect the carboxylic acid functionality of a cephalosporin while reactions involving other functional sites are carried out. Such carboxylic

20 acid protecting groups are noted for their ease of cleavage and for their ability to protect the acid from unwanted reactions. Such groups are thoroughly described by E. Haslam in Protective Groups in Organic Chemistry, Chapter 5. Any such group may be used, of course. The

25 preferred groups, however, are C_1-C_4 alkyl, C_4-C_6 t-alkyl, C_5-C_8 t-alkenyl, benzyl, methoxybenzyl, diphenylmethyl, phthalimidomethyl, succinimidomethyl or trichloroethyl.

 Similarly, the term protected hydroxy refers

30 to groups formed with a hydroxy group such as formyloxy,

2-chloroacetoxo, benzyloxy, diphenylmethoxy, triphenylmethoxy, phenoxy-carbonyloxy, t-butoxy and methoxymethoxy. Other accepted hydroxy-protecting groups, such as those described by C. B. Reese in chapter 3 of Protective Groups in Organic Chemistry will be understood to be included in the term protected hydroxy.

Since the process of this invention is carried out in an acid medium, any acid-labile groups which may be on the starting compound will be attacked. Such groups include, for example, the widely used trimethylsilyl protecting group. Acid-labile groups should be avoided in the practice of this invention, unless it is desired to remove them from the starting compound.

The term C_1-C_4 alkanoyloxy includes groups such as formyloxy, acetoxy, propionyloxy and butyryloxy. The term C_1-C_4 alkylcarbamoyloxy includes N-methylcarbamoyloxy, N-propylcarbamoyloxy, N-i-butylcarbamoyloxy and the like groups.

The pyridinio and substituted pyridinio groups, and the pyridinio chlorides and bromides, are groups comprising a pyridine ring joined through its nitrogen, and having three double bonds, so that the nitrogen atom is in the quaternary form.

The term C_1-C_4 alkylsulfonamido refers to groups such as methylsulfonamido, ethylsulfonamido, isopropylsulfonamido and t-butylsulfonamido.

Formation of esters of cephalosporin acids is a routine expedient in the art, for instance, as taught by U.S. Patent 3,632,850. The pNB esters are usually formed at a relatively early stage in the synthesis of

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the cephalosporin, and the compound is carried through synthetic steps in the pNB ester form. The ester may be formed, for example, by simple contact of a cephalosporin acid with p-nitrobenzyl bromide in any convenient solvent at ambient temperature. It may also be advantageous to form the pNB ester of a penicillin, especially a penicillin 1-oxide, and transform the penicillin into a cephalosporin by one of the well-known ring expansion techniques. The cephalosporin ester so made may then be subjected to additional steps to form the desired compound, and finally deesterified by the process of this invention to obtain the anti-biotically active cephalosporin acid.

A particularly preferred group of compounds includes those wherein R^1 is chloro, and those wherein R^1 is $-CH_2SR^{10}$.

The most preferred products of the present process are 7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, 7-(D-2-amino-2-phenylacetamido)-3-chloro-3-cephem-4-carboxylic acid, 7-(tetrazol-1-ylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid, and 7-(2-phenyl-2-hydroxyacetamido)-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

The electrolytic cells used for the process of this invention are the conventional types now known in the electrochemical art. This invention does not provide and does not need any new cells or other equipment. Some discussion of electrolytic cells will, however, be given.

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An electrolytic cell of the type used for electrolytic reductions has a working electrode, sometimes called the cathode, at which the reduction takes place. The working electrode is maintained at a potential which is negative with respect to the auxiliary electrode, or anode, at which only electrolyte reactions should take place. A reference electrode is usually also used. The reference electrode, at which no reactions should take place, supplies a reference point from which the potential of the working electrode is measured. A typical and frequently-used reference electrode is the saturated calomel electrode; others are the mercury/mercuric chloride electrode and the silver/silver chloride electrode. The reference electrode is electrically connected to the working fluid through a conductive bridge or a porous junction.

Cells are very often divided into compartments, so that each of the electrodes is immersed in fluid which is physically separated from the fluids of the other compartments, but is electrically connected to them. Such division of the cell is optional in the context of the present invention, unless the compound to be reduced bears a group which can be electrically oxidized, such as the compounds in which R is 4-hydroxyphenylacetyl. In general, groups having oxygen substitution on an aromatic ring are likely to be readily oxidized. The oxidizability of the starting compound may be readily determined by running a voltammogram on the auxiliary electrode in a positive direction with respect to the reference electrode.

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Figure 1 in the accompanying drawing is included to illustrate a typical voltammogram which results when a system adapted to the practice of this invention is subjected to an increasing negative
5 potential. The bottom axis, labeled E, measures the potential applied to the working electrode of the cell, compared to the reference electrode, and the potential is increasingly negative as one progresses to the right along the E axis.

10 The vertical axis, labeled i, indicates current flow through the cell, from the secondary electrode to the working electrode, and increases as one proceeds up the i axis.

A typical voltammogram curve is shown in
15 Figure 1. The curve is drawn in the usual manner, by slowly subjecting the system to increasingly negative potential, measuring the current at each potential, and plotting current against potential. The voltammogram shown represents a compound which has two groups
20 subject to electrolytic reduction.

The first reduction occurs at the point of the E-i curve between A and B. Point A marks the initial onset of current flow of the first reduction, and point B marks the initial onset of current flow of
25 the second reduction.

Point C indicates the onset of background discharge, which is the point where the solvent-electrolyte system begins to break down in an uncontrolled electrolysis, discharging hydrogen.

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The presence of inflection points, such as are shown in the figure, indicates that one or more oxidizable groups are present and that a divided cell is necessary, so that the auxiliary electrode is physically separated from the working fluid which contains the compound.

The arrangement of electrolytic cells, the construction of electrodes, and the materials which may be effectively used as dividers are all part of the common knowledge of the electrochemical art, and may easily be learned by reference to text books and journal articles. Particularly useful text books which may be mentioned include Organic Electrochemistry, M. M. Baizer, Editor, Marcel Dekker, Inc., New York (1973), and Technique of Electroorganic Synthesis, N. L. Weinberg, Editor, John Wiley and Sons, New York (1974).

Working electrodes for use in the process of this invention are made of carbon, mercury, tin, aluminum, silver, copper, lead, chromium, zinc, nickel or cadmium. The preferred working electrodes are mercury, silver and lead. The electrodes should be rather highly purified, as is normally the case in electrochemistry. The form of the electrode is not important; it may be solid sheet, gauze or cloth, a basket of shot, or a fluidized bed of particles, with equally good results. The electrode may also be made of an inert substrate plated with the electrode metal, or it may be made in the form of a sheet of the electrode composition, wrapped with gauze of the same composition to increase the electrode area.

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The auxiliary electrode does not participate in the reductive process, and so it may be made of any suitable substance which is not attacked by the oxidative side of the electrolytic process. Auxiliary electrodes are most often made of the noble metals, especially platinum, or of carbon. Platinum oxide, or platinum coated with platinum oxide, is the preferred anode composition. Lead oxide, silver oxide and such metallic oxides are also usable auxiliary electrode compositions.

It is most effective to arrange the cell so that the distance between the auxiliary electrode and the working electrode is everywhere the same, and is as small as possible. The relationship is desirable in all electrolytic processes, to maximize current flow and minimize temperature rise caused by the resistance of the fluid to the flow of current.

The process of this invention is carried out in an acidic working fluid, which is made acid by the addition of an acid having a pK_a of 0 or less, determined in water, preferably sulfuric acid or hydrochloric acid. Other strong acids such as phosphoric acid, nitric acid, p-toluenesulfonic acid and the like may also be used.

The acid is necessary to give up protons to the reaction at the working electrode, and also to keep the working fluid acid, because the products are unstable in basic conditions. Since the reduction is a 4-electron process, the working fluid must contain at least four moles of acid per mole of compound to be

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reduced. Greater amounts of acid, even up to ten or twenty moles per mole of compound, may be used if desired.

5 If an undivided cell is used, the fluid in contact with both the working electrode and the auxiliary electrode will be the same. If the cell is divided, however, the working fluid will undoubtedly be different from the fluid in the auxiliary electrode compartment.

10 The working fluid used in this invention is a mixture containing up to about 50% water, preferably from about 10% to about 50% water. The organic portions of the working fluid may be either water-miscible or water-immiscible. It is preferred to use a water-miscible solvent, so that the working fluid is a homo-
15 geneous solution.

Suitable water-miscible organic solvents include the amides, especially dimethylformamide and dimethylacetamide, acetone, the water-miscible alkanols, such as methanol, ethanol and propanol, and tetra-
20 hydrofuran.

If a water-immiscible solvent is used in the working fluid, the choice of solvents is extremely broad, because any solvent may be used which is not reduced at the working electrode. Especially desirable
25 solvents include the halogenated solvents, such as dichloromethane, 1,1,2-trichloroethane, chloroform, chlorobenzene, 1,1,1-trichloroethane and the like. Other immiscible solvents which may advantageously be used include the ketones including methyl ethyl ketone,
30 methyl butyl ketone and methyl isobutyl ketone, to

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mention only those which are economically available in commerce, the aromatic solvents such as benzene, toluene and the xylenes, the alkanes such as pentane, hexane and the octanes, the alcohols such as phenol, the butyl alcohols and the like, and ethers such as diethyl ether, diisopropyl ether and hexahydropyran.

When a water-immiscible solvent is used, the working fluid necessarily consists of two distinct phases. The acid remains in the aqueous phase, of course, and it is necessary to provide an electrolyte for the solvent phase of the working fluid. Such electrolytes are commonly used in the electrochemical art, and are preferably chosen from the class of tertiary amine salts. Useful electrolytes for this purpose include, for example, tetraethylammonium perchlorate, tetrabutylammonium perchlorate, benzotributylammonium chloride, benzyltriethylammonium bromide, benzyltriethylammonium chloride, methyltributylammonium iodide, tribenzylethylammonium p-toluenesulfonate, and the like electrolytes.

The same organic electrolytes are used when the working fluid is non-aqueous, if the acid is immiscible with the solvent.

If the process of this invention is to be carried out in a divided cell, the divider may be made of any of the materials commonly used in electrochemistry for the purpose. Especially useful dividers are made from the ion exchange membranes, especially those which can pass cations. Dividers may also advantageously be made of finely porous substances such as ceramic mem-

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branes and sintered glass membranes. Such porous dividers may be made permeable to ions, but not to the fluids themselves, by sealing the membranes with a conductive gel, of which a typical example is agar gel saturated with an ionic substance such as, for example, potassium sulfate.

When the auxiliary electrode occupies a cell compartment by itself, it is immersed in a conductive fluid. If the divider is a porous membrane, it is advisable to provide an auxiliary electrode fluid which is compatible with the working fluid, such as an aqueous solution of the mineral acid used in the working fluid. If the cell divider is porous only to ions, then the auxiliary electrode fluid may be any convenient conductive fluid, such as dilute aqueous solutions of ionizable salts and acids.

The temperature of the process is from about 0°C. to about 75°C., preferably from about 0°C. to about 30°C.

The potential of the working electrode, or the potential between the working electrode and the auxiliary electrode, may be controlled in various ways. The most effective and precise way to control the potential is to use a reference electrode, with its junction to the working fluid placed as physically close as possible to the working electrode. The desired potential for the process is determined from examination of a voltammogram of the system, and the potential between the working electrode and the auxiliary electrode is adjusted to give the desired constant potential between the reference electrode and the

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working electrode. This method of control is much more effective than control by the overall voltage between the working electrode and the auxiliary electrode, because that voltage depends on the condition of the dividing membrane, if any, the concentration of the acid in the working fluid, and the concentration of the compound to be reduced in the working fluid.

Similarly it is relatively inefficient to control the system by means of the current flow between the auxiliary electrode and the working electrode, because the current flow is directly dependent on the concentration of the compound to be reduced, as well as upon the physical condition of the electrodes and of the divider. However, when an individual reduction has been thoroughly studied and the relationship between current, time and concentration is known, controlled-current electrolysis can be used for production of repeated batches.

Thus, the best way to control the system is by the potential between a reference electrode and the working electrode, and the control most advantageously is provided by an automatic instrument which constantly senses that potential and adjusts the voltage between the working electrode and auxiliary electrode accordingly. Such instruments are now readily available; one maker of them is Princeton Applied Research, Inc., Princeton, N.J., U.S.A.

As has been briefly discussed above, the potential for operating the process of this invention with any given combination of electrodes, working fluid

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and compound is determined according to the routine method of the electrochemical art, by running a voltammogram of the system. It has been found, in performing voltammograms of many compounds of the formula described above, that the first current plateau corresponds to the reduction of the nitro group of the p-nitrobenzyl group of these compounds. Accordingly, it is selectively possible to reduce that nitro group without affecting other portions of the compound. Once the nitro group has been reduced, the benzyl ester group spontaneously hydrolyzes from the compound, producing the antibiotic cephalosporin acid.

It is not possible, of course, to name a precise potential range for the operation of the process of this invention, since the potential for every system will necessarily be different. It has been observed, however, that the potential of the working electrode for reductions according to this process is from about -0.3 volt to about -1 volt, relative to a saturated calomel reference electrode, in the majority of systems which have been used.

The reduction of this invention appears to be a 4-electron process, and so the reduction of a gram-mole of compound requires 385,948 coulombs. The length of time necessary to pass this amount of current necessarily depends upon the overall resistance of the cell and the effective area of the electrodes.

Electrolytic cells usually require good agitation, and the process of this invention is typical in this respect. It has been found advisable to

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provide enough agitation of the working fluid to keep the surface of the electrode thoroughly swept, so that a fresh supply of compound to be reduced is constantly supplied to the working electrode. Further, when a
5 water-immiscible solvent is used in the working fluid, it is necessary to agitate the fluid sufficiently well to keep the two phases of the working fluid intimately mixed in the form of fine droplets.

The electrochemical art has long known that
10 electrolytic processes are carried out more advantageously in flow cells than in batch electrolytic cells, in general. A flow cell is an electrolytic cell arranged for the constant passage of the working fluid through the cell. The cell volume may be quite small,
15 and the current density rather high, to achieve the desired extent of reaction in a single pass through the cell, or the flow rate may be lower and the volume higher, with the expectation that a number of passes through the cell will be necessary. In either event,
20 the flow cell is operated continuously with no interruptions for filling and emptying the cell, and the associated operations of product isolation and temperature control are carried on outside the cell.

Flow cells are set up just as are batch
25 cells, except for the necessary provisions for entry and exit of the working fluid. A flow cell may be divided, if necessary, in the usual manner. It is often possible to design a flow cell with the electrodes spaced advantageously close to each other,
30 because the agitation of the working fluid is provided

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by its own flow velocity and it is unnecessary to provide for mechanical agitation of the cell. For example, a flow cell is often built in the form of a plate-and-frame filter press, with the electrodes in sheet form, clamped between the frames.

The concentration of the compound to be reduced in the working fluid is widely variable and is limited only by the solubility of the compound. Of course, it is most economical to use relatively high concentrations, in order to obtain the maximum effect from the solvents used in the process. However, work-up of the fluid and isolation of the product from it is frequently more difficult when highly concentrated working fluids are used. Accordingly, it has not been advantageous in practice to use concentrations of compound in the working fluid higher than about 20% weight/volume.

The cephalosporin acid is recovered from the working fluid by a conventional isolation procedure. Typically, the working fluid is diluted with a large amount of dilute mineral acid, such as 1-normal hydrochloric acid, and the dilute solution is extracted with ethyl acetate. In some cases, it is advantageous to back-extract the organic layer with additional dilute acid, to remove as much as possible of the organic portions of the working fluid. The organic layer is then evaporated under vacuum to obtain the product, which may be further purified, as by recrystallization, if desired.

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In isolating the product, it is separated from an impurity which is believed to be composed of polymers of the aminobenzyl moiety removed in the reduction. This polymeric impurity is formed in
5 deesterifications according to the prior art methods, as well. The use of dimethylformamide as the solvent in the working fluid makes the isolation problem much easier, and back-extraction of the first organic layer obtained in the isolation steps, with dilute aqueous
10 acid, is very useful in removing the polymeric impurity.

The following examples are included to assist the reader in understanding the process of this invention, and to assure that a skilled electrochemist can carry out any desired process of this invention.
15 The products of the examples were identified by instrumental analytical techniques, as will be explained in the individual examples. Some products were made repeatedly by different embodiments of the process of the invention, and in such cases, the products were
20 often merely identified by thin-layer chromatography (TLC) or by nuclear magnetic resonance (NMR) analysis as identical to the original product, and were not otherwise isolated or identified.

Much of the data in the following examples
25 has been tabulated, to condense the information, and the compounds made by the processes to be described will be identified by the following code. It will be understood, of course, that in all cases the starting compound was the corresponding p-nitrobenzyl ester.

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1. 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid
2. 7-(2-phenyl-2-aminoacetamido)-3-methyl-3-cephem-4-carboxylic acid
- 5 3. 7-phenoxyacetamido-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid
4. 7-(2-thienylacetamido)-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid
5. 7-(2-t-butoxycarbonylamino-2-phenylacetamido)-7-methoxy-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid
- 10 6. 7-(2-hydroxy-2-phenylacetamido)-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid
7. 7-phenoxyacetamido-3-(5-methyl-1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid
- 15 8. 7-(2-thienylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid
9. 7-(tetrazol-1-ylacetamido)-3-(5-methyl-1,3,4-thiadiazol-2-ylthiomethyl)-3-cephem-4-carboxylic acid
- 20 10. 7-[2-(2-triphenylmethylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-exomethylenecepham-4-carboxylic acid
11. 7-phenylacetamido-3-chloro-3-cephem-4-carboxylic acid
- 25 12. 7-[2-(2-triphenylmethylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-chloro-3-cephem-4-carboxylic acid
13. 7-phenoxyacetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid
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14. 7-(2-thienylacetamido)-3-benzoyloxymethyl-3-cephem-4-carboxylic acid
15. 7-(2-thienylacetamido)-3-(2-methyltetrazol-5-ylaminomethyl)-3-cephem-4-carboxylic acid
- 5 16. 7-(2-thienylacetamido)-3-(4-carbamoylpyridinio-methyl)-3-cephem-4-carboxylic acid, bromide
17. 7-(2-thienylacetamido)-3-(4-chlorophenylthio-methyl)-3-cephem-4-carboxylic acid
18. 7-(2-thienylacetamido)-3-(benzo[4,5-a]-1,2,3-triazol-1-yloxymethyl)-3-cephem-4-carboxylic acid
- 10 19. 7-(2-thienylacetamido)-3-methoxycarbonylmethyl-thiomethyl-3-cephem-4-carboxylic acid
20. 7-(2-thienylacetamido)-3-t-butoxycarbonylmethyl-thiomethyl-3-cephem-4-carboxylic acid
- 15 21. 7-(2-thienylacetamido)-7-methoxy-3-carbamoylthio-methyl-3-cephem-4-carboxylic acid
22. 7-(2-thienylacetamido)-3-fluoromethyl-3-cephem-4-carboxylic acid
23. 7-(2-thienylacetamido)-3-(1-carboxymethyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid
- 20 24. 7-(2-thienylacetamido)-3-(5-amino-4-cyanopyrimidin-2-ylthiomethyl)-3-cephem-4-carboxylic acid
25. 7-[2-(2-triphenylmethylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(6-hydroxy-4-methyl-5-oxo-1,2,4-triazin-3-ylthiomethyl)-3-cephem-4-carboxylic acid, 1-oxide
- 25 26. 7-(2-thienylacetamido)-3-(1H-pyrazolo[3,4-d]-pyrimidin-4-ylthiomethyl)-3-cephem-4-carboxylic acid
- 30 27. 7-(2-thienylacetamido)-3-(1H-pyrazolo[4,3-d]-pyrimidin-7-ylthiomethyl)-3-cephem-4-carboxylic acid

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28. 7-(2-thienylacetamido)-3-(4-benzylcarbonyloxy-aminomethyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid
- 5 29. 7-(2-thienylacetamido)-3-(5-carbamoyl-4-methyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid
30. 7-(2-t-butoxycarbonylamino-2-phenylacetamido)-3-(5-carbamoyl-4-methyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid
- 10 31. 7-[2-(2-triphenylmethylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-carbamoyl-4-methyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid
- 15 32. 7-[2-(2-triphenylmethylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(4-methyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid
33. 7-(2-thienylacetamido)-3-(5-aminomethyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid
- 20 34. 7-(2-thienylacetamido)-3-(5-ethoxycarbonyl-4-methyl-1,2,4-triazol-3-ylthiomethyl)-3-cephem-4-carboxylic acid

25 The examples which follow are arranged in groups, according to the variations in the operating conditions under which they were run. Most of the operating data are tabulated.

The first group of examples were run in small batch electrolytic cells, having volumes from about 10 to 100 ml.

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Examples 1-29

In these examples, the working fluid was comprised of 90% by volume of dimethylformamide, and 10% by volume of 12N sulfuric acid. The working electrode was a toroidal mercury pool having an area, in various experiments, of from 14 to 20 cm.². The auxiliary electrode was a loop of platinum wire, parallel to the surface of the working electrode, and separated from the working electrode by a fine glass frit. The reference electrode, in all experiments, was a saturated calomel electrode, with its junction placed physically as close as possible to the surface of the working electrode. In some experiments, the cell was an H-type cell with the three electrodes in separate tubes, separated by fine glass frits. An automatic potentiostat was used to control the potential between the working electrode and the reference electrode, and in most cases no measurement of overall voltage of the cell was made. The current flows recorded in the table below indicate the approximate maximum current flow at the beginning of the experiment; the current flow, of course, declined steadily as the starting compound was used up.

Many experiments were run at controlled temperatures; room temperature experiments are indicated by R.T.

Operating conditions which were not recorded by the operator are indicated by N.R.

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In the tables below, the total time of the experiment is indicated, to the nearest 10 minutes, and the total amount of current passed is expressed in terms of a percentage of the theoretical amount of current necessary to accomplish a 4-electron reaction.

The products were isolated by diluting the working fluid with a large amount of dilute aqueous acid, usually hydrochloric acid, and extracting the diluted solution several times with portions of ethyl acetate. The organic layers were then back-extracted several times with additional portions of dilute aqueous acid, and evaporated to dryness under vacuum to obtain the product. In general, the products were not further purified. Physical-chemical characterizing data for the products is tabulated after the tables showing the operating conditions of the experiments.

The working fluid in all of the experiments was kept free of air by bubbling argon slowly through it.

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Table 1

Example	Compound	G./ml.	Temp.	Potential	Max. Current	Time	Total Current	Product Yield
1	1	1/50	25°C.	-0.45 v.	140 ma	330 min	105%	0.62 g.
2	1	4/40	25°	-0.5	150	420	94%	2.16
3	1	4/40	25°	-0.45	400	480	94%	2.17
4	1	2.5/25	25°	-0.4	300	470	106%	1.22
5	3	4/40	25°	-0.4	400	470	87%	2.31
6	3	2/24	25°	-0.5	300	320	80%	1.11
7	4	0.4/	25°	-0.4	400	180	61%	0.16
8	5	9.9/100	25°	-0.4	400	90	86%	3.85
9	6	.25/15	R.T.	-0.4	40	150	15%	0.12
10	9	.2/15	R.T.	-0.5	30	220	100%	0.09
11	10	1.7/30	25°	-0.4	N.R.	N.R.	N.R.	0.09
12	11	.1/15	R.T.	-0.8	75	20	132%	0.07
13	12	2/30	10°	-0.45	150	320	N.R.	0.4
14	13	4.9/60	25°	N.R.	400	530	96%	1.8
15	14	0.06/30	25°	-0.35	9	220	76%	N.R.
16	18	0.1/25	25°	-0.375	24	230	95%	0.04

Table 1 cont.

Example	Compound	G./ml.	Temp.	Potential	Max. Current	Time	Total Current	Product Yield
17	20	0.84/35	25°C.	-0.38 v.	130 ma	220 min	102%	0.575 g.
18	21	0.08/30	25°	N.R.	N.R.	N.R.	N.R.	0.035
19	22	0.04/10	22°	-0.4---0.6	N.R.	N.R.	N.R.	N.R.
20	23	0.68/30	25°	-0.4	160	180	102%	N.R.
21	26	0.5/37	25°	-0.4	54	330	100%	0.12
22	28	0.51/35	25°	-0.5	50	370	N.R.	0.094
23	29	0.2/10	21°	-0.5	40	210	80%	0.04
24	30	0.36/25	25°	-0.4	60	330	93%	N.R.
25	30	0.91/35	25°	-0.5	60	370	79%	0.275
26	31	1.5/40	25°	-0.45	N.R.	N.R.	N.R.	0.15
27	31	1.5/40	25°	-0.475	N.R.	N.R.	N.R.	0.1
28	33	0.5/30	25°	-0.475	60	270	78%	N.R.
29	34	0.2/10	21°	-0.4	30	220	107%	0.1

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The following NMR features were observed in analysis of the compounds prepared in the examples above.

- 5 Compound 1, 60 MHz instrument in DMSO_d₆; δ 2.12 (s); 3.53 (broad s); 5.15 (d, J = 4.5 Hz); 5.71 (dd, J = 8 Hz and 4.5 Hz); 8.98 (d, J = 8 Hz); 4.68 (s); 6.8-7.6 (m)
- 10 Compound 3, 60 MHz instrument in DMSO_d₆; δ 3.73 (broad s); 3.95 (s); 4.31 (broad s); 4.63 (s); 5.10 (d, J = 4.5 Hz); 5.75 (dd, J = 8 Hz and 4.5 Hz); 6.70-7.5 (m); 9.13 (d, J = 8 Hz)
- 15 Compound 4, 100 MHz instrument in DMSO_d₆; δ 3.70 (ABq), 3.77 (s); 3.93 (s) 4.31 (ABq); 5.08 (d, J = 4.5 Hz); 5.67 (dd, J = 8 Hz and 4.5 Hz); 6.85-7.42 (m); 9.12 (d, J = 8 Hz)
- Compound 5, 100 MHz instrument in DMSO_d₆; δ 1.91 (s); 3.38 (s); 3.46 (ABq); 3.90 (s); 4.25 (ABq); 5.06 (s); 5.34 (d, J = 8 Hz); 7.2-7.6 (m); 9.47 (broad s)
- 20 Compound 6, 60 MHz instrument in DMSO_d₆; δ 3.68 (broad s); 3.93 (s); 4.30 (broad s); 5.06 (d, J = 4.5 Hz); 5.11 (broad s); 5.71 (dd, J = 8 Hz and 4.5 Hz); 7.18-7.65 (m); 8.68 (d, J = 8 Hz)
- 25 Compound 9, 60 MHz instrument in DMSO_d₆; δ 2.17 (s); 3.69 (ABq); 4.38 (ABq); 5.12 (d, J = 4.5 Hz); 5.37 (s); 5.72 (dd, J = 8 Hz and 4.5 Hz); 9.36 (s); 9.50 (d, J = 4.5 Hz)
- 30 Compound 10, 100 MHz instrument in CDCl₃; δ 3.45 (ABq); 4.23 (s); 5.10 (s); 5.23 (broad s); 5.38 (d, J = 4.5 Hz); 5.62 (dd, J = 8 Hz and 4.5 Hz); 6.6 (s); 7.1 (s); 7.35 (s); 8.03 (d, J = 8 Hz)

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- Compound 11, 60 MHz instrument in CDCl_3 plus acetone d_6 ; δ 3.68; 3.75; 5.00; 5.80; 7.33; 7.85
- Compound 12, 60 MHz instrument in CDCl_3 ; δ 3.57 (ABq); 4.09 (s); 5.10 (d, $J = 4.5$ Hz); 5.78 (dd, $J = 8$ Hz and 4.5 Hz); 6.76 (s); 7.35 (m); 7.65 (d, $J = 8$ Hz)
- Compound 13, 60 MHz instrument in $\text{DMSO}-d_6$; δ 2.03 (s); 3.60 (broad s); 4.63 (s); 4.90 (ABq); 5.10 (d, $J = 4.5$ Hz); 5.76 (dd, $J = 8$ Hz); 6.7-7.5 (m); 9.08 (d)
- Compound 14, 100 MHz instrument in acetone d_6 ; δ 3.77 (ABq); 3.90 (s); 5.19 (d, $J = 4.5$ Hz); 5.26 (ABq); 5.85 (dd, $J = 8$ Hz and 4.5 Hz); 6.85-8.15 (m); 8.05 (d, $J = 8$ Hz)
- Compound 18, 60 MHz instrument in $\text{DMSO}-d_6$; δ 3.69 (broad s); 3.93 (broad s); 5.14 (d, $J = 4.5$ Hz); 5.39 (broad s); 5.72 (dd, $J = 8$ Hz and 4.5 Hz); 6.85-7.42 (m); 7.50-8.12 (m); 9.18 (d, $J = 8$ Hz)
- Compound 20, 100 MHz instrument in $\text{DMSO}-d_6$; δ 1.41 (s); 3.22 (ABq); 3.51 (ABq); 3.67 (broad s); 3.76 (s); 5.09 (d, $J = 4.5$ Hz); 5.63 (dd, $J = 8$ Hz and 4.5 Hz); 6.95 (m); 7.35 (m); 9.09 (d, $J = 8$ Hz)
- Compound 21, no analysis
- Compound 22, 60 MHz instrument in acetone d_6 ; δ 3.71 (broad s); 3.98 (s); 5.36 (d, $J = 4.8$ Hz); 5.25 (d, $J = 4.5$ Hz); 5.78 (dd, $J = 8$ Hz and 4.5 Hz); 6.9-7.5 (m); 8.16 (d, $J = 8$ Hz)
- Compound 23, 100 MHz instrument in $\text{DMSO}-d_6$; δ 3.66 (ABq); 3.75 (s); 4.33 (ABq); 5.05 (d, $J = 4.5$ Hz); 5.3 (s); 6.95 (m); 7.35 (m); 9.12 (d, $J = 8$ Hz)

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Compound 26, 60 MHz instrument in DMSO_d₆; δ 3.53 (ABq); 3.78 (s); 4.53 (ABq); 5.13 (d, J = 4.5 Hz); 5.71 (dd, J = 8 Hz and 4.5 Hz); 6.85-7.40 (m); 8.15 (s); 8.90 (s); 9.16 (d, J = 8 Hz);

5 Compound 28, 60 MHz instrument in DMSO_d₆; δ 3.73 (broad s); 3.85 (s); 4.28 (ABq); 4.40 (d, J = 6 Hz); 5.13 (d, J = 4.5 Hz); 5.15 (s); 5.76 (dd, J = 8 Hz and 4.5 Hz); 7.41 (s); 7.78 (t, J = 6 Hz); 9.20 (J = 8 Hz);

10 Compound 29, 60 MHz instrument in DMSO_d₆; δ 3.68 (broad s); 3.78 (s); 3.77 (s); 4.19 (ABq); 5.07 (d, J = 4.5 Hz); 5.66 (dd, J = 8 Hz and 4.5 Hz); 6.85-7.40 (m); 7.83 (broad s); 8.17 (broad s); 9.14 (d = 8 Hz)

15 Compound 30, 60 MHz instrument in DMSO_d₆; δ 1.36 (s); 3.59 (broad s); 3.77 (s); 4.14 (broad s); 4.98 (d, J = 4.5 Hz); 5.31 (d, J = 9 Hz); 5.67 (dd, J = 8 Hz and 4.5 Hz); 7.15-7.50 (m); 7.82 (broad s) 8.16 (broad s); 9.17 (d, J = 8 Hz)

20 Compound 31, 360 MHz instrument in DMSO_d₆; δ 3.64 (ABq); 3.77 (s); 3.81 (s); 4.18 (ABq); 5.09 (d, J = 4.5 Hz); 5.68 (dd, J = 8 Hz and 4.5 Hz); 6.71 (s); 7.2-7.4 (m); 7.86 (broad s); 8.21 (broad s); 8.84 (s); 9.58 (d, J = 8 Hz)

25 Compound 33, no analysis

30 Compound 34, 60 MHz instrument in DMSO_d₆; δ 1.33 (t, J = 7 Hz); 3.68 (broad s); 3.78 (q, J = 7 Hz); 4.23 (broad s); 4.39 (q, J = 7 Hz); 5.07 (d, J = 4.5 Hz); 5.66 (dd, J = 8 Hz and 4.5 Hz); 6.85-7.40 (m); 9.14 (d, J = 8 Hz)

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Examples 30-40

5 The following examples report experiments run
according to the method described above, except that,
in these examples, the auxiliary electrode was separated
from the working electrode by a frit coated with an
electrically conductive gel. In some experiments, the
gel was formed from agar made with an ionizable salt
solution, and in other experiments, the frit was coated
with methyl cellulose gel made conductive in the same
10 manner.

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Table 2

Example	Compound	G./ml.	Temp.	Potential	Max. Current	Time	Total Current	Product Yield
30	1	1/35	10°C	-0.4 v	N.R.	180 min	N.R.	0.62 g.
31	1	1/25	25°	-0.4	200 ma	370	113%	0.54
32	7	4.1/50	R.T.	-0.5	N.R.	280	78%	2.06
33	7	1.5/40	R.T.	-0.5	130	120	N.R.	0.84
34	15	0.93/30	25°	-0.3---0.45	N.R.	N.R.	N.R.	0.1
35	16	0.4/25	25°	N.R.	30	230	77%	N.R.
36	17	0.1/35	25°	-0.4	13	320	100%	0.035
37	19	0.63/24	25°	-0.5---0.7	23	150	90%	N.R.
38	24	0.8/30	25°	-0.4	N.R.	N.R.	91%	0.38
39	27	1.62/25	25°	-0.45	200	330	97%	0.27
40	8	1/25	25°	-0.4	150	330	92%	0.6

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Compound 7, 60 MHz instrument in DMSO_d₆; δ 2.67 (s); 3.68 (ABq); 4.37 (ABq); 4.61 (s); 5.12 (d, $J = 4.5$ Hz); 5.71 (dd, $J = 8$ Hz and 4.5 Hz); 6.8-7.4 (m); 9.09 (d, $J = 8$ Hz)

5 Compound 15, 100 MHz instrument in DMSO_d₆; δ 3.51 (broad s); 3.76 (s); 4.09 (s); 4.22 (ABq); 5.04 (d, $J = 4.5$ Hz); 5.62 (dd, $J = 8$ Hz and 4.5 Hz); 6.85-7.4 (m); 9.07 (d, $J = 8$ Hz)

10 Compound 16 identified only by TLC

Compound 17, 60 MHz instrument in acetone d_6 ; δ 3.71 (ABq); 3.93 (s); 4.23 (ABq); 5.13 (d, $J = 4.5$ Hz); 5.80 (dd, $J = 8$ Hz and 4.5 Hz); 6.83-7.73 (m); 8.08 (d, $J = 8$ Hz)

15 Compound 19, 100 MHz instrument in DMSO_d₆; δ 3.34 (s); 3.61 (s); 3.67 (s); 3.76; 5.12 (d, $J = 4.5$ Hz); 5.66 (dd, $J = 8$ Hz and 4.5 Hz); 6.85-7.40 (m); 9.09 (d, $J = 8$ Hz)

20 Compound 24, 60 MHz instrument in DMSO_d₆; δ 3.68 (broad s); 3.78 (s); 4.20 (ABq); 5.13 (d, $J = 4.5$ Hz); 5.66 (dd, $J = 8$ Hz and 4.5 Hz); 6.95 (m); 7.35 (m); 7.93 (broad s); 8.40 (s)

25 Compound 27, 60 MHz instrument in DMSO_d₆; δ 3.5 (broad s); 5.63 (dd, $J = 8$ Hz and 4.5 Hz); 6.98 (m); 7.37 (m); 8.45 (s); 8.78 (s); 9.08 (d, $J = 8$ Hz)

30 Compound 8, 60 MHz instrument in DMSO_d₆; δ 2.63 (s); 3.70 (ABq); 3.80 (s); 4.41 (ABq); 5.14 (d, $J = 4.5$ Hz); 5.73 (dd, $J = 8$ Hz and 4.5 Hz); 6.90-7.50 (m); 9.16 (d, $J = 8$ Hz)

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Examples 41-42

The experiments reported in these examples
were carried out in the same manner as the experiments
of examples 1-29, except that the working and auxiliary
5 electrodes were separated by an ion exchange membrane.

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Table 3

<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>	<u>Total Current</u>	<u>Product Yield</u>
41	25	0.4/37	25°C.	-0.34 v.	20 ma	150 min	34%	0.09 g.
42	32	1/30	17°	-0.45	90	220	96%	0.12

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Compound 25, no analysis

Compound 32, 100 MHz instrument in CDCl_3 ; δ 3.65 (s);
3.70 (ABq); 4.0 (s); 4.25 (broad s); 5.12 (d, $J = 4.5$
Hz); 5.82 (dd); 6.70 (s); 7.15-7.50 (m); 8.33 (s);

5

Example 43

The experiment of this example was also
carried out according to the methods described in the
text of examples 1-29, except that the working and
10 auxiliary electrodes in this experiment were not
separated.

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Table 4

<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>	<u>Total Current</u>	<u>Product Yield</u>
43	3	0.6/50	25°C.	-0.4 v.	500 ma	N.R.	N.R.	0.15 g.

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Example 44

5 The experiment of this example was also
carried out according to the process as described in
the text of examples 1-29, except that the working
electrode was lead, rather than mercury.

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Table 5

<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>	<u>Total Current</u>	<u>Product Yield</u>
44	3	0.6/85	25°C.	-0.8 v.	100 ma	370 min	N.R.	N.R.

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Example 45

The method described in the text of Examples 1-29 was used for this experiment also, except that the working fluid was made up of 90% dimethylformamide and 10% of 24N sulfuric acid.

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Table 6

<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>	<u>Total Current</u>	<u>Product Yield</u>
45	5	11/100	25°C.	-0.4 v.	350 ma.	N.R.	N.R.	4 g.

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Examples 46-50

5 In the following examples, the working fluids
were mixtures of dimethylformamide and hydrochloric
acid. Various amounts and concentrations of hydro-
chloric acid were used in the various experiments, as
detailed in the table below. In other respects, the
cells and methods were as described in the text intro-
10 ducing Examples 1-29, except that in some experiments,
the working and auxiliary electrodes were separated by
a frit coated with a gel, as described in the intro-
duction to Examples 30-40. The table below indicates
the experiments in which a gel-coated frit was used.

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Table 7

Example	Cpd.	Gel- frit	HCl	HCl Conc.	G./ml	Temp.	Potential	Max. Current	Time	Total Current	Product Yield
46	1		10%	11N	1/50	R.T.	-0.65 v.	N.R.	N.R.	105%	0.72 g.
47	2	X	10%	con.	0.2/80	25°C.	-0.55	40 ma.	250 min	115%	N.R.
48	2		20%	con.	5/50	0°	-0.6	1.5 a.	N.R.	N.R.	N.R.
49	2		10%	con.	5/50	15°	-1.2	650 ma.	270	95%	3.2
50	7	X	10%	2N	0.5/80	R.T.	-0.45	N.R.	370	84%	0.24

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Compound 2, 60 MHz instrument in TFAd_1 (trifluoroacetic acid); δ 2.31 (s); 5.18 (d, $J = 4.5$ Hz); 5.53 (s); 5.76 (d, $J = 4.5$ Hz); 7.60 (s)

Example 51

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The working fluid used in this example was composed of 40 ml. of dimethylformamide and 10 ml. of pH 5.0 sodium acetate buffer, with sufficient p-toluenesulfonic acid added to the mixture to make it 1.8N. The working electrode was a pool of mercury, and the counter electrode was a platinum wire, immersed in the working fluid with no electrode separation. The reference electrode was saturated calomel.

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Table 8

<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>	<u>Total Current</u>	<u>Product Yield</u>
51	1	1/50	25°C.	-0.85 v.	90 ma	320 min	78%	0.31 g.

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Example 52

5 The working fluid in the experiment of this example was dimethylformamide, which was 0.1-molar in tetraethylammonium perchlorate and contained about 35 mg./ml. of p-toluenesulfonic acid. The mercury pool working electrode was separated from the platinum auxiliary electrode by a glass frit.

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Table 9

<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>	<u>Total Current</u>	<u>Product Yield</u>
52	1	1/50	25°C.	-0.6 v.	80 ma	320 min	80%	0.54

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Example 53

5 The working fluid in this experiment was a mixture of 45% of tetrahydrofuran and 55% of an 0.1M solution of pH 4.6 buffer. The measured pH of the working fluid, with the compound dissolved in it, was 5.5, and the pH of the working fluid was held at 5.5 throughout the experiment by the use of a pH controller which added 2N sulfuric acid as necessary.

10 The working electrode was mercury, and the auxiliary electrode was a platinum wire, separated from the working electrode by a fine glass frit coated with potassium sulfate-saturated agar. The reference electrode was saturated calomel, with the porous junction placed as close as possible to the working
15 electrode.

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<u>Table 10</u>						
<u>Example</u>	<u>Compound</u>	<u>G./ml.</u>	<u>Temp.</u>	<u>Potential</u>	<u>Max. Current</u>	<u>Time</u>
53	3	0.45/90	25°C.	-0.73 v.	25 ma	250 min
						57%
						<u>Product Yield</u>
						0.17

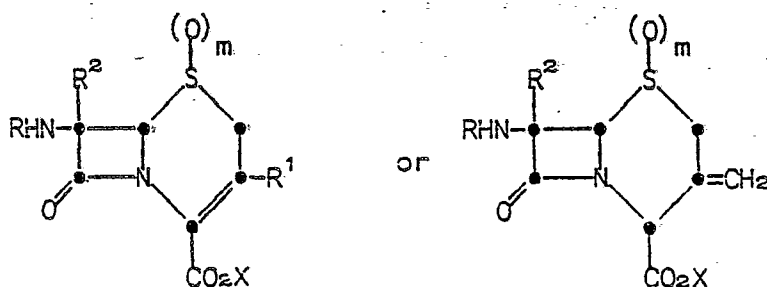
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CLAIMS

1. A process for removing the pNB ester protecting group from a cephalosporin 4-carboxylic acid pNB ester and thereby liberating the free cephalosporin 4-carboxylic acid;
- 5 characterized in that the pNB ester is electrolytically reduced in an acidic liquid medium comprising from about 0 to about 50% water, an acid having a pK_a determined in water of 0 or below, the amount of said
- 10 acid being at least four moles per mole of the compound to be reduced, and an organic solvent substantially inert to electrolytic reduction, at the working electrode of an electrolytic cell, said working electrode sub-
- 15 stantially comprising carbon, mercury, tin, aluminum, silver, copper, lead, chromium, zinc, nickel or cadmium, at a temperature from about 0°C. to about 75°C., at a potential in a range from about the potential of the initial onset of current flow of the first reduction to about the potential of the initial onset of current
- 20 flow of the second reduction.

2. A process according to claim 1 for preparing a compound of the formula



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wherein X is hydrogen;

m is 0 or 1;

 R^2 is hydrogen or methoxy; R is hydrogen or $-\text{COR}^3$;

5 R^3 is hydrogen, C_1 - C_3 alkyl, halomethyl, benzyloxy, 2,2,2-trichloroethoxy, t-butoxy, R^4 , $R^4-(\text{O})_n-\text{CH}_2-$, $R^4-\text{CH}(R^5)-$, $R^6-\text{CH}_2-$, or



wherein R^7 is hydrogen or C_1 - C_3 alkyl and R^8 is hydrogen or an amino-protecting group;

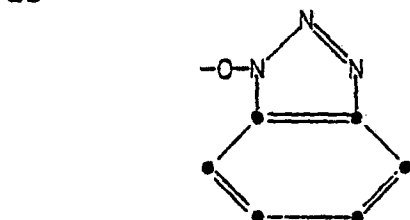
15 R^4 is cyclohexadienyl or phenyl, or cyclohexadienyl or phenyl substituted with one or two halo, hydroxy, protected hydroxy, aminomethyl, protected amino-methyl, C_1 - C_4 alkyl or C_1 - C_4 alkoxy groups;

n is 0 or 1;

20 R^5 is hydroxy, protected hydroxy, amino, protected amino, carboxy or protected carboxy;

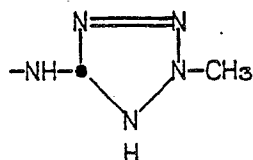
 R^6 is 2-thienyl, 2-furyl, 5-tetrazolyl or 1-tetrazolyl; R^1 is chloro, C_1 - C_3 alkyl or $-\text{CH}_2\text{R}^9$;

25 R^9 is C_1 - C_4 alkanoyloxy, benzoyloxy, fluoro, chloro, carbamoyloxy, C_1 - C_4 alkylcarbamoyloxy,



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5

pyridinio, pyridinio substituted with C_1-C_4 alkyl, C_1-C_4 alkanoyl, carbamoyl, C_1-C_4 alkyl-carbamoyl, chloro, fluoro, hydroxy or trifluoromethyl, or the corresponding pyridinio chlorides or bromides, or $-S-R^{10}$;

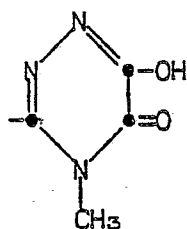
10

R^{10} is $-CH_2CO_2(C_1-C_4 \text{ alkyl})$, carbamoyl, phenyl, phenyl substituted with one or two chloro, fluoro, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkylsulfonamido or trifluoromethyl groups;

15

triazol-3-yl unsubstituted or substituted with one or two groups independently selected from C_1-C_3 alkyl, $-CO_2(C_1-C_4 \text{ alkyl})$, $-CONH_2$ and $-CH_2NHOCO(\text{benzyl or } C_1-C_4 \text{ alkyl})$;

20



25

tetrazol-1-yl or tetrazol-5-yl substituted with one or two groups independently selected from C_1-C_4 alkyl and $-CH_2CO_2(C_1-C_4 \text{ alkyl or hydrogen})$; 4-cyano-5-aminopyrimidin-2-yl, or 5-methyl-1,3,4-thiadiazol-2-yl;

30

provided that n is 0 when R^4 is cyclohexadienyl; by electrolytically reducing a compound of the above formula wherein X is p-nitrobenzyl.

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3. A process according to claim 1 or 2, wherein the acidic liquid medium comprises from about 10% to about 50% water.

4. A process according to any one of claims 1 to 3 wherein the organic solvent is water-miscible.

5. A process according to any one of claims 1 to 4, wherein the working electrode comprises silver, lead or mercury.

6. A process according to any one of claims 1 to 5, wherein the potential is controlled by means of a reference electrode.

7. A process according to any one of claims 2 to 6 wherein the cephalosporin 4-carboxylic acid formed is a compound wherein R^1 is chloro, methyl or $-CH_2SR^{10}$.

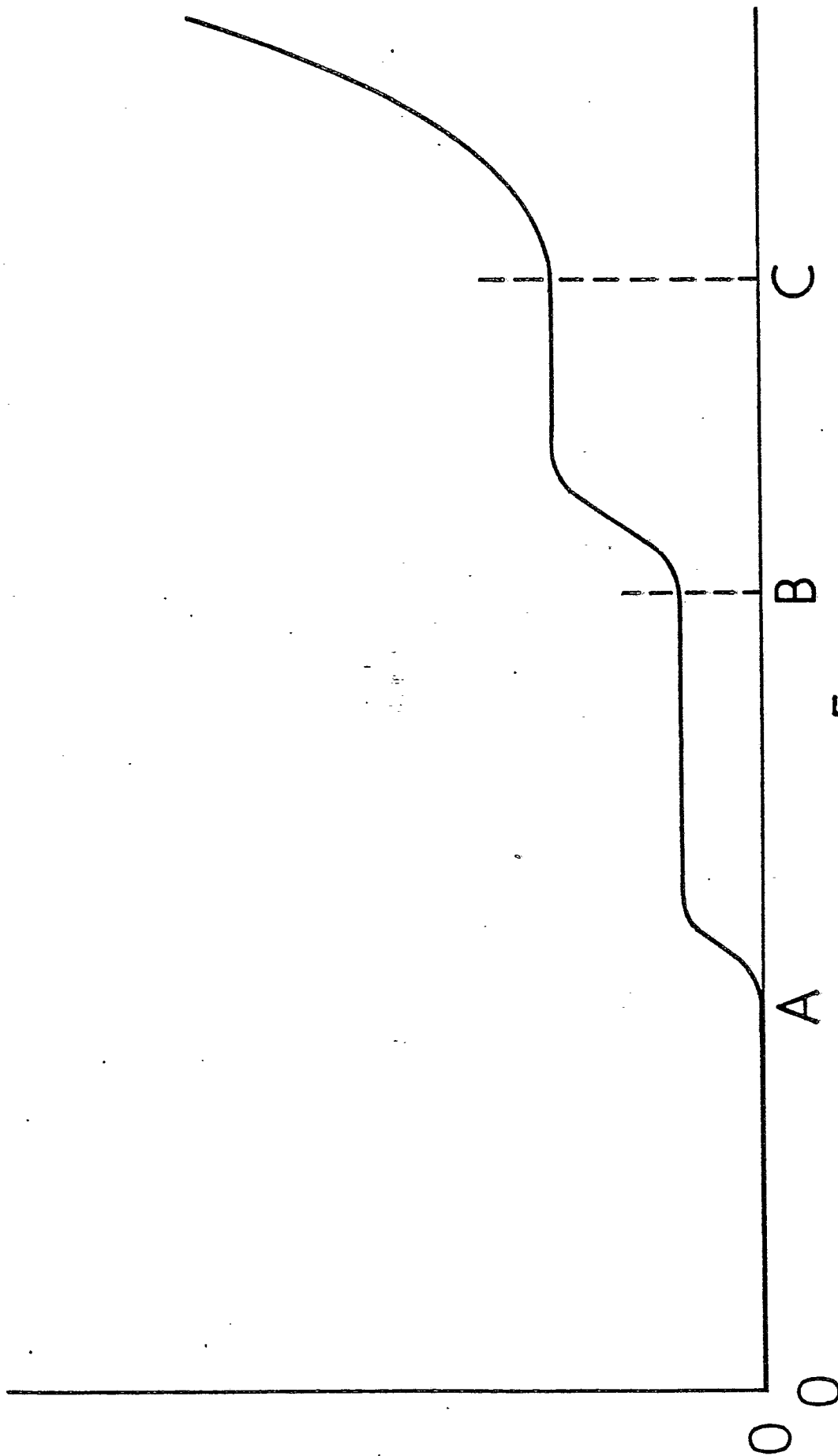
8. A process according to claim 7 wherein R^{10} is a triazol-3-yl, tetrazol-1-yl, tetrazol-5-yl or thiadiazol-2-yl group.

9. A process according to any one of claims 1 to 8, for preparing 7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid.

10. A process according to any one of claims 1 to 8, for preparing 7-(D-2-amino-2-phenylacetamido)-3-chloro-3-cephem-4-carboxylic acid.

11. A cephalosporin 4-carboxylic acid recovered from the working fluid produced by a process according to any of claims 1 to 10.

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FIG. 1



European Patent
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EUROPEAN SEARCH REPORT

Application number

EP 81 30 1187

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	US - A - 4 042 472 (D.A. HALL)		C 25 B 3/04 C 07 D 501/00
DA	US - A - 3 632 850 (W.L.GARBRECHT)		
A	TECHNIQUES OF CHEMISTRY, vol. V, Part II, Technique of Electro-organic Synthesis, Edited by N.L. Weinberg Electrochemical reduction of nitro-compounds, pages 137-140 John Wiley & Sons		TECHNICAL FIELDS SEARCHED (Int. Cl. ³) C 25 B 3/00 3/04
A	ANGEW. CHEM. INT. ED. ENGL., vol. 15 (1976), no. 5 V.G. MAIRANOVSKY: "Electro-deprotection/Electrochemical removal of protecting groups", pages 281-292 * Paragraph 3.3., pages 285-286 table 2, page 290 *		
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
			&: member of the same patent family. corresponding document
X The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of the search 03-08-1981	Examiner DEL PIERO