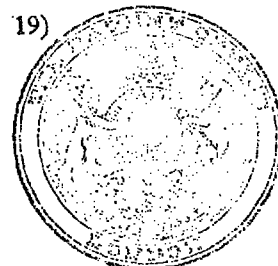


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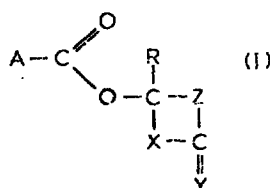
(72) Inventors HARRY FERRES and JOHN PETER CLAYTON

(54) PENICILLINS AND CEPHALOSPORINS

(71) We, BEECHAM GROUP LIMITED, a British Company, of Beecham House Great West Road, Brentford, Middlesex, England do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel class of esters of penicillins and cephalosporins which, upon oral administration are absorbed into the bloodstream where they are split by enzymic action to release the antibacterially active parent penicillin or cephalosporin.

According to the present invention there is provided a class of compounds of formula (I) and pharmaceutically acceptable acid addition salts of those compounds of formula (I) which contain a basic nitrogen atom:—

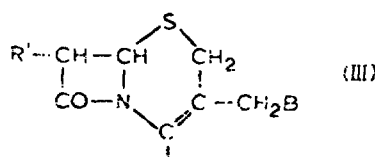
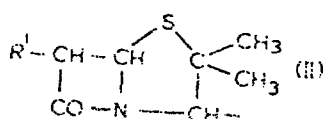


wherein X and Y are the same or different and each represents oxygen or sulphur;

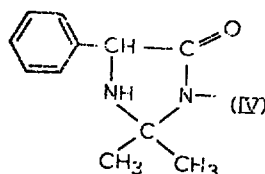
Z represents a straight or branched, saturated or unsaturated divalent hydrocarbon radical having from 1 to 7 carbon atoms in which two adjacent carbon atoms are joined in a carbocyclic ring system which may carry one or more substituents;

R represents hydrogen or an alkyl alkenyl, alkynyl, aryl or aralkyl group, or a functional substituent;

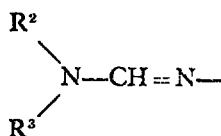
A represents a group of formula (II) or (III):—



wherein B represents hydrogen or an acetoxy group and R¹ is an organic acylamino group, a group of formula IV:—

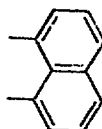


or a group of formula (V):—



wherein R² and R³ each represent a C₁ to C₂ alkyl group, or R² and R³ taken together with the nitrogen atom to which they are attached form a monocyclic ring, the foregoing definition of compounds of formula (I) being subject to the proviso that when A is a group of formula (II) R¹ is not the D(-)-α-aminophenylacetamido group when R is hydrogen, X and Y are both oxygen and Z is a 1,2-phenylene group.

Preferably both X and Y are oxygen and preferably R¹ is an organic acylamino group. By way of example, and subject to the above proviso, Z may be a 1,2-phenylene group which may carry one or more substituents such as alkoxy, nitro or halogen substituents in the phenyl ring. Z may also be a group of formula



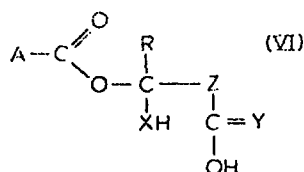
Also by way of example, the group R in formula (I) above may be C₁ to C₂ alkyl, e.g. methyl or ethyl; lower alkenyl, e.g. vinyl or allyl; lower alkynyl e.g. ethynyl; aryl e.g. phenyl; or aralkyl e.g. benzyl. R may also be a functional group such as a hydroxy, alkoxy, halogen, amino or carboxyl group. Preferably R is hydrogen or a methyl or phenyl group.

The radical A in formula (I) is a 6-substituted penam-3 or 7-substituted 3-cephem-4 radical. When R¹ is an organic acylamino group, specific examples include any of the acylamino side chains found in known antibacterially active penicillins and cephalosporins. Foreexample, R¹ in formulae II or III may be phenylacetamido; 2- or 3- thienylacetamido; *para*-hydroxy-α-amino-phenylacetamido; phenoxyacetamido, α-amino-phenylacetamido; α-amino-2(or 3-) thienylacetamido, α-carboxyphenylacetamido; α-sulphophenylacetamido; α-azidophenylacetamido or α-guanidinophenylacetamido, but other examples of suitable acylamino groups will be found later in this specification in the specific examples.

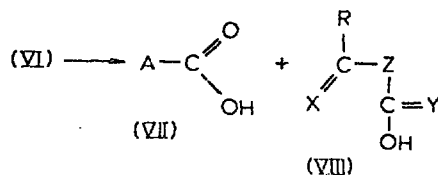
It will be clear that when the acylamino group R¹ contains an asymmetric carbon atom, the compounds of this invention can exist in two optically active forms. This invention includes the pure epimers as well as mixtures of epimers.

In formulae (II and (III) R¹ may also be a group of formula (V). Preferably R² and R³ in formula (V) are both methyl or together represent the divalent radical —CH₂(CH₂)₄CH₂—.

In the presence of human and animal serum, the esters of this invention are split to release the parent penicillanic or cephalosporanic acid. Although this invention is not limited by any theory of mechanism, we believe that non-specific esterases in the serum split the molecule to give an unstable intermediate (VI):



The intermediate (IV) then undergoes spontaneous decomposition as follows:—

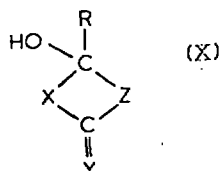


The esters of this invention may be prepared by esterification of the carboxyl group of the corresponding penicillanic acid or cephalosporanic acid.

Thus, the invention also provides a process for the preparation of compounds (I) which process comprises reacting a compound of formula (IX):—



or a reactive esterifying derivative thereof, in which formula A is as defined with respect to formula (I) with a compound of formula (X).



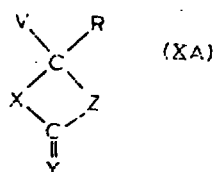
or a reactive esterifying derivative thereof, in which formula X, Y, Z and R are as defined in formula (I).

By the term "reactive esterifying derivative" in relation to compounds (IX) and (X) above, we mean derivatives of (IX) and (X) which when reacted together take part in a condensation reaction with the consequent formation of an ester linkage.

Many methods of esterification using several different combinations of reactive esterifying derivative are known from the literature. For example, the esterification reaction defined above may be achieved by reacting a compound of formula (IXA)



wherein A is as defined with reference to formula (I) above, with a compound of formula (XA)



wherein R, X, Y and Z are as defined in relation to formula (I), under conditions which cause the elimination of the elements of compound UV with the consequent formation of the ester of formula (I); the symbols U and V in formulae (IXA) and (XA) being such that U represents hydrogen or a salt-forming ion and V represents a hydroxy group, an alkylsulphonyloxy group, an arylsulphonyloxy group or a halogen atom; or U represents an organic acyl group and V represents a hydroxy group.

When the group R¹ in radical A of compound (IX) contains a free amino group, it is preferable that the amino group should be protected prior to the esterification reaction. More will be said about specific protecting groups which can be employed later.

The esterification procedures outlined above are all specific applications of esterification methods known in the literature. Usually it will be found satisfactory to react compound (IXA) wherein U is a sodium or potassium ion; with compound (XA) wherein V is a halogen atom, especially bromine or chlorine.

When U in compound (IXA) is hydrogen or a salt-forming ion and V in compound (XA) is a hydroxy group, the reaction is generally slow and inconvenient. Preferably, in such cases the hydroxy group V in compound (XA) is best converted to an alkylsulphonyl or arylsulphonyl ester, since this gives a smoother reaction. In this case, the presence of a base is usually necessary to achieve high yields.

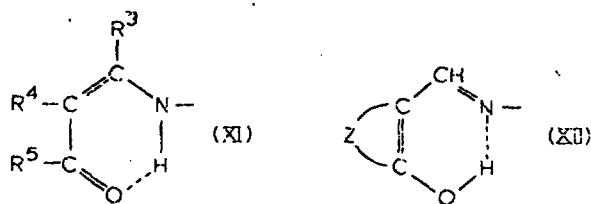
In the case where the group U in reagent (IXA) is an organic acyl group, it will be clear that (IXA) is simply a mixed anhydride, the acyl group may be one of a wide variety of aliphatic or aromatic acyl groups but generally the alkoxy carbonyl groups (e.g. C₂H₅OCO- group) are satisfactory.

Another reactive esterifying derivative of compound (IX) above is the acid halide, particularly the acid chloride. This compound may be reacted with the hydroxy compound (X) in the presence of an acid binding agent to prepare the desired ester of this invention.

When the group R¹ in radical A of compound (IX) or (IXA) contains a free amino group, this group should be protected before the esterification reaction.

Examples of protected amino groups include the protonated amino group (NH₃⁺) which after the acylation reaction can be converted to a free amino group by simple neutralisation; the benzyloxycarbonylamino group (X = NH.CO₂CH₂Ph) or substituted benzyloxycarbonylamino groups which are subsequently converted to NH₂ by catalytic hydrogenation; and various groups which after the acylation reaction regenerate the amino group on mild acid hydrolysis. (Alkaline hydrolysis is not generally useful since hydrolysis of the ester group takes place under alkaline conditions).

Examples of the group X which may subsequently be converted to NH₂ by mild acid hydrolysis include enamine groups of general formula (XI) or tautomeric modifications thereof, and α-hydroxyarylidene groups of general formula (XII) or tautomeric modifications thereof:—

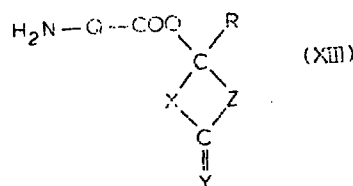


In structures (XI) and (XII) the dotted lines represent hydrogen bonds. In structure (XI) R³ is a C₁ to C₇ alkyl group, R⁴ is either a hydrogen atom or together with R³ completes a carbocyclic ring, and R⁵ is a C₁ to C₇ alkyl, aryl, or C₁ to C₇ alkoxy group. In structure (XII) Z represents the residue of a substituted or unsubstituted benzene or naphthalene ring.

An example of a "protected amino" group which can be converted to NH₂ after the esterification reaction is the azido group. In this case, the final conversion into NH₂ may be brought about by either catalytic hydrogenation or electrolytic reduction.

An alternative method of making compounds of this invention of formula (I) wherein the R¹ group in radical A is an acylamino group, is by N-acylation of the corresponding 6-aminopenam or 7-aminocephem.

Thus, in another of its embodiments, this invention provides a method for the preparation of compounds of formula (I) wherein the group R¹ in radical A is an acylamino group, which method comprises reacting a compound of formula (XIII)



or a silyl derivative thereof wherein $\text{H}_2\text{NQ}-$ represents a 6-amino-penam-3 radical, a 7-amino-3-methyl-ceph-3-em-4 radical or a 7-amino-3-acetoxymethyl-ceph-3-em-4 radical and R, X and Y are as defined in formula (I), with a reactive N-acylating derivative of a compound of formula (XIV)



wherein R_a^1 is an organic acyl group which may carry a protected amino group, removing the silyl group, if present, by hydrolysis or alcoholysis, and, if a protected amino group is present, optionally converting it to a free amino group under acid or neutral conditions.

By the term "silyl derivative" of the compound (XIII) we mean the product of the reaction between compound (XIII) and a silylating agent such as a halotrialkylsilane, a dihalodialkylsilane, a halotrialkylsilane, a dihalodialkoxysilane or a corresponding aryl or alkyl silane and compounds such as hexamethyldisilazane. In general halotrialkylsilanes are preferred, especially trimethylchlorosilane. The silylated derivatives of the ester (XIII) are extremely sensitive to moisture and hydroxylic compounds, and after reaction with the reactive derivative of compound (XIV), the silyl group of the intermediate acylated compound can be removed by hydrolysis or alcoholysis.

A reactive N-acylating derivative of the acid (XIV) is employed in the above process. The choice of reactive derivative will of course be influenced by the chemical nature of the acyl group R^1 . Thus, when R^1 is acid stable or carries an acid stable group, such as the protonated amino group NH_3^+ or the azido group, it is often convenient to convert the acid (XIV) into an acid halide for example by treating it with thionyl chloride or phosphorus pentachloride to give the acid chloride.

Such reagents would however be avoided when R^1 is an acid labile group or carries an acid labile group, e.g. of type (XI) or (XII). In such cases it is often convenient to make use of a mixed anhydride. For this purpose particularly convenient mixed anhydrides are the alkoxy-formic anhydrides, which are conveniently prepared by treating an alkali metal or tertiary amine salt of the acid (XIV) with the appropriate alkyl chloroformate in an anhydrous medium at or below room temperature.

Other reactive N-acylating derivatives of the acid (XIV) include the reactive intermediate formed on reaction *in situ* with a carbodiimide or carbonyl-diimidazole.

The esters of formula (XIII) used in the above process can be prepared, though in poor yield by direct coupling of 6-aminopenicillanic acid or 7-amino cephalosporanic or 7-amino-desacetoxyccephalosporanic acid with the appropriate bromolactone in the presence of base. With this process some epimerisation at C_6 or C_7 may occur and the process may not be entirely satisfactory.

The esters of formula (XIII) are also new compounds and they are valuable intermediates in the process of this invention.

Compounds (XIII) can also be prepared by coupling an N-protected derivative of 6-aminopenicillanic acid or 7-amino cephalosporanic or 7-aminodesacetoxyccephalosporanic acid (e.g. the triphenylmethyl derivative) with the appropriate 4-bromolactone and thereafter removing the protecting group (e.g. by mild acid hydrolysis in the case of the triphenylmethyl derivative). Alternative types of N-protected 6-aminopenicillanic acid are the 6-acylaminopenicillanic acids. Techniques for the removal of the 6-acyl side chain from benzylpenicillin and phenoxymethyl penicillin, for example, are well documented (cf. British Patent No. 1,189,022) and generally involve treating an ester of the 6-acylaminopenicillanic acid with PCl_5 to form an imino chloride bond on the 6-amido nitrogen atom, then treating the imino chloride with an alcohol to form an imino ether and then hydrolysing the imino bond to form the 6-aminopenicillanic acid ester. In the present case, it is possible to start from the appropriate ester of penicillin G or penicillin V (prepared for example reaction of the sodium or potassium salt of the penicillin with the appropriate bromolactone and cleave the acyl side chain to prepare the ester of 6-aminopenicillanic acid.

Similarly, alternative types of N-protected 7-amino cephalosporanic acid are the 7-acylaminocephalosporanic acids. Techniques for the removal of the 7-acyl side chain from cephalosporins are well known, and in the present case, it is possible to start with the appropriate ester of a 7-acylamino cepham, (e.g. Cephalosporin C) and remove the acyl side chain to form the ester of 7-aminocephalosporanic acid or 7-amino-desacetoxy-cephalosporanic acid. Since the compounds of this invention are split in the human body to release the parent penicillin or cephalosporin, the invention also includes pharmaceutical compositions, particularly those suitable for oral administration, comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

The following Examples illustrate methods for the preparation of some of the compounds of this invention. In these Examples all temperatures are in °C unless otherwise stated, and the word "Celite" is a Registered Trade Mark.

EXAMPLE 1.

(a) PREPARATION OF 5,6-DIMETHOXY-PHTHALIDE

Method

3,4-Dimethoxybenzoic acid (12.5 g; 0.0687 mole) was heated on a water bath for 12 hours with formaldehyde solution (37—41%; 13.75 ml) and conc. hydrochloric acid (50 ml).

The black mixture was diluted with its own volume of water, cooled and shaken and the suspension decanted from the black oil deposited on the sides of the flask. The decanted liquid was left overnight to crystallise. The solid was filtered, washed with water and recrystallised from ethanol (Yield 4.5 g).

The black oily residue in the reaction vessel was extracted with hot sodium hydroxide solution, treated with charcoal and acidified with hydrochloric acid, cooled and left to crystallise. The solid was filtered, washed with water and recrystallised from ethanol (Yield 1.6 g).

Total Yield 6.1 g. 45.8%

M.P. 155—6°C (Lit. 155—7°C)

Method 2.

3,4-Dimethoxybenzoic acid (100 g; 0.55 mole) was heated with formaldehyde solution (37—41%; 256 ml) and conc. hydrochloric acid (836 ml) on a water bath with efficient stirring for 2 hours.

The black liquid was allowed to cool and was decanted from a small amount of black solid, into water (5 l.). The solid was filtered off, washed with sodium carbonate solution and then with water, dried and recrystallised from ethanol.

Yield 41.2 g. 38.6%

(b) PREPARATION OF 3-BROMO-5,6-DIMETHOXY-PHTHALIDE

5,6-Dimethoxyphthalide (5.82 g; 0.03 mole), N-bromosuccinimide (5.34 g; 0.03 mole) and α -azo-isobutyronitrile (0.1 g.) were gently refluxed in dry carbon tetrachloride (150 ml) for 2 hours.

The solution was cooled, the succinimide filtered off and the solvent removed in *vacuo* leaving a yellow solid, which was washed with 40—60° petrol, and dried.

This solid was used immediately and not stored as it is unstable in moist air.

Yield 7.6 g (93%)

(c) 6[D(-)- α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID 5,6-DIMETHOXY-PHTHALIDYL ESTER, HYDROCHLORIDE

Potassium salt of 6[D(-)-N-(1-methoxycarbonyl-propen-2-yl)- α -aminophenyl-acetamido] penicillanic acid (10.7 g; 0.0212 mole) and 3-bromo-5,6-dimethoxyphthalide (5.8 g; 0.021 mole) were stirred overnight in anhydrous acetone (200 ml). The mixture was filtered and evaporated in *vacuo* to a foam.

The foam was dissolved in ethyl acetate (210 ml) and washed with N/2 sodium bicarbonate solution (70 ml), water (70 ml) and saturated brine (2 x 70 ml). The solution was again evaporated in *vacuo* to a foam.

The foam was dissolved in acetone (105 ml) and water (70 ml) added and the pH maintained at 1.9 on the pH-meter by dropwise addition of 5N hydrochloric acid (3.9 ml). The acetone was removed from the clear solution by evaporation in *vacuo* and the resultant aqueous liquid extracted with ethyl acetate (105 ml). The organic layer, on separation, was diluted with 40—60° petrol (75 ml) and extracted with water at pH 3.0 (30 ml).

The combined aqueous extracts were treated with solid sodium chloride (35 g) and stirred for 1 hour. The resulting oil was separated, dissolved in acetone (120 ml), dried over anhydrous magnesium sulphate and filtered into stirring, dry, ether (3 l.).

The precipitated solid was filtered, washed with dry ether and sucked dry to yield the ester as a fine, white, electrostatic powder.

Yield: 3.5 g. (28.6%)

EXAMPLE 2.

(a) 6-METHOXYPHTHALIDE

6-Methoxyphthalide was prepared by the reaction of m-anisic acid with formaldehyde solution and conc. hydrochloric acid by the method of Chakravarti and Perkin, J. Chem Soc. 1929, 199, except that heating was only continued till all solid had dissolved, not for as long as 1 hour. Further reaction time was found to result in substitution in the phthalide 5-position.

Yield: 13%

(b) 3-BROMO-6-METHOXYPHTHALIDE

3-Bromo-6-methoxyphthalide was prepared using the same procedure as described in Example 1 (b).

(c) 6[D(-)- α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID 6-METHOXYPHTHALIDYL ESTER, HYDROCHLORIDE

The potassium salt of 6[D(-)-N-(1-methoxy-carbonylpropen-2-yl)- α -aminophenylacetamido] penicillanic acid (15.5 gm, 0.0308 mole) and 3-bromo-6-methoxyphthalide (7.5 gm, 0.0308 mole) were stirred overnight in dry acetone (200 ml). The mixture was filtered through Celite and evaporated *in vacuo* to a foam, which was dissolved in ethyl acetate (210 ml) and washed with N/2 sodium bicarbonate solution (70 ml), water (70 ml) and saturated brine (2 x 70 ml). The solution was again evaporated to a foam *in vacuo* and then dissolved in acetone (105 ml) and water (70 ml) added. The pH was then maintained at ca 1.9 on the pH meter by dropwise addition of 5N hydrochloric acid (4.9 ml). The acetone was removed from the clear solution *in vacuo* and the aqueous layer extracted with ethyl acetate (105 ml).

The aqueous layer was treated with solid sodium chloride (25.9 gm) and stirred for $\frac{1}{2}$ hour. The resultant oil was separated and dissolved in isopropanol (38 ml) dried over anhydrous magnesium sulphate, filtered and poured slowly with stirring into dry ether (3 litres). The precipitated solid was filtered, washed with ether and dried.

Yield 9.9 gms. 58.5%

Hydroxylamine Assay 119.1%

EXAMPLE 3.

(a) 6-CHLORO-PHTHALIDE

Prepared by the action of sulphuryl chloride on phthalide in a melt of aluminium chloride (anhydrous) and sodium formate as in the German Patent No. 1,266,310.

(b) 3-BROMO-6-CHLORO-PHTHALIDE

6-Chlorophthalide (7.66 gms; 0.0452 mole) N-bromosuccinimide (8.1 gms; 0.0452 mole) and azobisisobutyronitrile (0.1 gm) were gently refluxed in dry carbon tetrachloride (150 ml) for 1 $\frac{1}{2}$ hours. On cooling, the succinimide was filtered off and the solvent removed *in vacuo* to leave a yellow solid, which was used immediately.

Yield 9.57 gms. 86.2%

(c) 6[D(-)- α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID 6-CHLORO-PHTHALIDYL ESTER, HYDROCHLORIDE

6[D(-)-N-(1-Methoxycarbonylpropen-2-yl)- α -aminophenylacetamido] penicillanic acid, potassium salt (22.9 gms; 0.0455 mole) and 3-bromo-6-chloro-phthalide (11.24 gms; 0.0455 mole) in dry acetone (350 ml) were stirred overnight.

The mixture was filtered through Celite and the solution evaporated *in vacuo* to a foam. The foam was dissolved in ethyl acetate (250 ml) and washed with N/2 sodium bicarbonate (100 ml), water (100 ml) and saturated brine (100 ml) and dried over anhydrous magnesium sulphate.

The solution was concentrated to ca. 50 ml. *in vacuo* and poured into vigorously stirring 40—60° petrol (3 l.). The solid was filtered, washed with petrol and dried,

giving the 6-chloro-phthalidyl ester of 6[D(-)N-(1-methoxycarbonyl-propen-2-yl)- α -aminophenyl acetamido] penicillanic acid as a light yellow solid.

Yield 15.3 gms. 55.8%

5 This ester was dissolved in acetone (175 ml) and water (150 ml) added. The pH was maintained at 1.8 on the pH meter by dropwise addition of 5N hydrochloric acid. The acetone was removed in vacuo and the aqueous solution extracted with ethyl acetate (30 ml). The aqueous solution was then salted with solid sodium chloride and the resulting oil separated, dissolved in acetone (50 ml) and dried over anhydrous magnesium sulphate. The solution was poured into vigorously stirring dry ether (3 l.) and the solid filtered, washed with ether and dried to give the 6-chloro-phthalidyl ester of 6-(D(-) α -aminophenylacetamido) penicillanic acid, hydrochloride.

10 Yield: 6.4 gms. 46.5%

Hydroxylamine Assay 109.8%

EXAMPLE 4.

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(a) 4,5,6-TRIMETHOXY-PHTHALIDE

Prepared by the action of formalin and concentrated hydrochloric acid on trimethyl gallic acid (3,4,5-trimethoxy-benzoic acid) by the method of King and King (J. Chem. Soc. 1942, 726--7).

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(b) 3-BROMO-4,5,6-TRIMETHOXY-PHTHALIDE

4,5,6-Trimethoxyphthalide (11.4 gms—0.05 mole), N-bromo-succinimide (8.9 gms; 0.05 mole) and azobisisobutyronitrile (0.1 gms) were refluxed gently in dry carbon tetrachloride (200 mls) for 2 hours. The solution was cooled, the succinimide filtered off and the solvent removed in vacuo, leaving a yellowish solid which fumed in the air.

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Yield: 14.7 gms; 97.1%

The solid was used immediately.

25

(c) 4,5,6-TRIMETHOXY-PHTHALIDE ESTER OF 6[D(-) α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID, HYDROCHLORIDE

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6[D(-)N-(1-methoxycarbonylpropen-2-yl)- α -aminophenylacetamido] penicillanic acid, potassium salt (24.6 gms; 0.0486 mole) and 3-bromo-4,5,6-trimethoxyphthalide (14.7 gms; 0.0486 mole) were stirred in acetone (250 ml) for 5 hours.

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The mixture was filtered through Celite and evaporated to a foam in vacuo. The foam was dissolved in ethyl acetate (300 ml) and washed with N/2 sodium bicarbonate solution (100 mls), water (100 mls) and saturated brine (2 $\times$ 100 ml). The solution was evaporated to a foam again and dissolved in acetone (100 ml) with water (70 ml). The pH was maintained at 1.9 on the pH meter by dropwise addition of 5N hydrochloric acid. The acetone was removed in vacuo and solid sodium chloride added to the residual aqueous layer and stirred for $\frac{1}{2}$ hour.

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The liquid was decanted from the precipitated solid and the latter dissolved in acetone, the solution dried over anhydrous magnesium sulphate and poured into dry stirring ether (4 l.). The solid was filtered, washed with ether and dried to give the 4,5,6-trimethoxyphthalidyl ester of 6[D(-) α -aminophenylacetamido] penicillanic acid, hydrochloride.

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Yield: 20.6 gms. 69.5%

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EXAMPLE 5.

(a) 6-BROMO-PHTHALIDE

Prepared by the action of bromine on phthalide in a melt of anhydrous aluminium chloride and urca as in the German Patent No. 1,266,310.

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(b) 3,6-DIBROMO-PHTHALIDE

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6-Bromophthalide (5.85 gms; 0.0275 mole), N-bromosuccinimide (4.89 gm; 0.0275 mole) and azo-bisbutyronitrile (0.1 gm) were gently refluxed in dry carbon tetrachloride (200 ml) for 2 hours. On cooling, the succinimide was filtered off and the solvent removed in vacuo to give an oil, which was used immediately.

(c) 6-BROMOPHTHALIDYL ESTER OF
6[D(-)- α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID,
HYDROCHLORIDE

6[D(-)-N-(1-methoxycarbonylpropen-2-yl)- α -aminophenylacetamido] penicil-
lanic acid potassium salt (13.9 gms; 0.0275 mole) and 3,6-Dibromophthalide (8 gm;
0.0275 mole) were stirred in dry acetone (200 ml) overnight. The solution was filtered
through Celite and evaporated in vacuo to a foam, which was dissolved in ethyl
acetate (200 ml). The solution was washed with N/2 sodium bicarbonate (100 ml),
water (100 ml) and saturated brine (2 $\times$ 100 ml). The solution was again evaporated
to a foam in vacuo and dissolved in ethyl acetate (30 ml) and poured into stirring
40—60° petrol giving the 6-bromo phthalidyl ester of 6[D(-)-N-(1-methoxycarbonyl-
propen-2-yl)- α -amino-phenylacetamido] penicillanic acid as a cream-coloured solid
which was filtered, washed with petrol and dried.

Yield: 10.6 gm. 58.3%

This ester was dissolved in acetone (120 ml) and water (105 ml) added. The
pH was maintained at 1.8 by dropwise addition of 5N hydrochloric acid on the pH
meter. The acetone was removed in vacuo and the aqueous solution extracted with
ethyl acetate (20 ml). The residual aqueous solution was salted with solid sodium
chloride and the resulting oil separated, dissolved in acetone (50 ml) and dried over
anhydrous magnesium sulphate. The solution was poured into vigorously stirring dry
ether (2.5 lit) and the solid filtered, washed with ether, and dried to give the 6-bromo-
phthalidyl ester of 6[D(-)- α -aminophenylacetamido] penicillanic acid, hydrochloride.

Yield: 4.2 gms. 43.7%

Hydroxylamine Assay 111.9%

EXAMPLE 6.

(a) PREPARATION OF 6-NITROPHTHALIDE

6-Nitrophthalide was prepared in 67.3% yield by the method of J. Tirouflet
Bull. Soc. Sci. Bretagne. Spec. No. 26, 7—122 (1951) m.p. 142°—3° (from litera-
ture m.p. = 143°).

(b) PREPARATION OF 2-HYDROXYMETHYL-5-NITRO-N,N-
DIMETHYLBENZAMIDE

To a stirred solution of 6-nitrophthalide (2 g) in ethanol (120 ml) at room
temperature was added dimethylamine (in ethanol 33.3% solution: 50 ml). After
stirring for 5 hours the solvent was evaporated off. The resulting gum was dissolved
in ethyl acetate. On addition of petrol 60°—80° a white solid crystallised out.

Yield: 1.77 g = 70.8% m.p. = 106°—7°

(c) PREPARATION OF 2-CARBOXY-4-NITROBENZALDEHYDE

To a solution of 2-hydroxymethyl-5-nitro-N,N-dimethylenzamide (17 g) in
glacial acetic acid (340 ml) was added chromium trioxide (17 g) in water (17 ml)
and glacial acetic acid (340-1). The reaction mixture was stirred at room temperature
for 5 minutes, and then poured into ice-water (2 litres). The aqueous was extracted
with chloroform (3 $\times$ 300 ml). The chloroform extracts were combined and neutralised
by washing with 10% sodium bicarbonate solution. The chloroform extracts were
then washed thoroughly with water and dried over magnesium sulphate. The solution
was then filtered and the solvent evaporated off to yield a gum.

Crude yield = 15.0 g.

The gum was the refluxed in 3N hydrochloric acid (150 ml) for 2½ hours. On
cooling a white solid crystallised out. This was filtered off and dried.

Yield = 5.6 g = 37.8% m.p. = 153°—4°

(d) PREPARATION OF 6-NITROPHTHALIDYL ESTER OF
BENZYL-PENICILLIN

To a suspension of benzylpenicillin sodium salt (7.12g : 0.02M) in dry methylene
dichloride (50 ml) at -5°C was added six drops of pyridine and ethyl chloroformate
(2.17g; 1.91 ml; 0.02M). The reaction mixture was stirred at -5°C for ½ hour by
which time the solution was almost clear.

A suspension of 2-carboxy-4-nitrobenzaldehyde (3.90 g; 0.02M) in dry methy-
lene dichloride (20 ml) was added at 5°C. After ½ hour the reaction mixture was
allowed to warm to room temperature, and then stirred for a further 4 hours.

The solution was then washed with 2% sodium bicarbonate solution (50 ml) and water (3 x 50 ml). The organic layer was dried over magnesium sulphate, filtered and the solvent evaporated off in vacuo.

The gum was dissolved in a small amount of ethyl acetate, filtered and dripped into excess petrol 40°—60°.

The resulting solid was filtered off and dried.

Yield = 1.6g = 15.7%

The bio-chromatogram showed two zones:—

$R_f = 0.95$ = 6-nitrophthalidyl ester of benzylpenicillin.

$R_f = 0.59$ = benzylpenicillin.

The I.R. and N.M.R. spectra were consistent with a mixture of benzylpenicillin and the 6-nitrophthalidyl ester of benzylpenicillin.

EXAMPLE 7.

(a) PERI-NAPHTHALDEHYDIC ACID

Prepared by the action of 30% potassium hydroxide solution on accnaphthene-quinone by the method of Fuson et al. (J. Amer. Chem. Soc. 71, 1870).

(b) PERI-NAPHTHALIDE

Prepared by the action of formalin and potassium hydroxide on peri-naphthaldehydic acid by the method of Fuson et al. (J. Amer. Chem. Soc. 71, 1870).

(c) 3-BROMO-PERI-NAPHTHALIDE

Peri-naphthalide (1.7 gms, 9.23 m.mole), N-bromo-succinimide (1.64 gms; 9.23 m.mole) and azoiso-butyronitrile (0.1 gm) were gently refluxed in dry carbon tetrachloride for 2 hours. The solution was cooled, the succinimide filtered off and the solvent removed in vacuo to leave the bromide which was used immediately.

Yield: 1.3 gms 53.5%

(d) PERI-NAPHTHALIDYL ESTER OF 6[D(-)- α -AMINO-PHENYLACETAMIDO] PENICILLANIC ACID, HYDROCHLORIDE

6[D(1)N-(1-methoxycarbonylpropen-2-yl)- α -aminophenylacetamido] penicillanic acid potassium salt (6.36 gms; 13.9 m.mole) and 3-bromo-peri-naphthalide (3.6 gms; 13.9 m.mole) were stirred in dry acetone overnight.

The mixture was filtered through Celite, evaporated in vacuo to a foam which was dissolved in ethyl acetate (100 ml) and washed with 1N sodium bicarbonate solution (50 ml), water (2 x 50 ml) and saturated brine solution (50 ml). The solution was again evaporated in vacuo and dissolved in acetone (50 ml) with water (40 ml) and the pH maintained at 1.8 by addition of 5N hydrochloric acid dropwise.

The acetone was removed under reduced pressure and the resulting aqueous solution salted with solid sodium chloride, precipitating a gummy solid. The liquid was decanted off and the residue dissolved in a little acetone, dried over anhydrous magnesium sulphate and poured into an excess dry, stirring ether. The precipitated solid was filtered, washed with dry ether and dried, to give an impure sample of the 6[D(-)- γ α -aminophenylacetamido] penicillanic acid peri-naphthalidyl ester, hydrochloride.

EXAMPLE 8.

(a) PREPARATION OF 2-THIOPHTHALIDE

o-Cyanobenzylbromide was converted to o-cyanobenzylthiocyanate using potassium thiocyanate in ethanol. This went in 96% yield by the method of A. W. Day and S. Gabriel, Berichte 1890 23 2478—89. o-Cyanobenzylthiocyanate was converted to o-cyanobenzylmercaptan using concentrated sulphuric acid in 93% yield, using the method of M. Renson and R. Collienne. Bull. Soc. Chim. Belges. 73. (5—6) 491—506 (1954). o-Cyanobenzylmercaptan was converted into 2-thiophthalide by the action of boiling water by the method of M. Renson etc. in 45% yield.

(b) PREPARATION OF 3-BROMO-2-THIOPHTHALIDE

To a solution of 2-thiophthalide (5.0 g; 0.033M) in dry carbon tetrachloride (100 ml) was added N-bromosuccinimide (5.72 g; 0.033M) and a catalytic amount of *tert*-azoiso-butyronitrile. The reaction mixture was refluxed gently for 1 hour, and

then cooled. The solution was filtered and the solvent evaporated off. The product was recrystallised from cyclohexane.

Yield = 4.5 g. (70.11%).

(c) PREPARATION OF 2-THIOPHTHALIDYL ESTER OF
6[D(-)- α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID,
HYDROCHLORIDE

A suspension of potassium salt of 6[D(-)-N-(1-methoxycarbonylpropen-2-yl)- α -aminophenylacetamido] penicillanic acid (10.07 g. 0.02M) was stirred at 0°C in dry acetone (100 ml). To this was added 3-bromo-2-thiophthalide (4.58 g. 0.02M) in dry acetone (20 ml). The reaction mixture was allowed to warm to room temperature and stirred for a further 5 hours. The reaction mixture was then filtered and the solvent allowed to evaporate off in vacuo. The resulting gum was dissolved in ethyl acetate (100 ml) and vigorously stirred. Water (100 ml) was added and the pH adjusted to 2.0 with 5N hydrochloric acid. The organic layer was retained and washed with water (50 ml) and brine. The ethyl acetate solution was dried over magnesium sulphate, filtered and evaporated in vacuo. The resulting gum was triturated with petroleum ether 40–60° and the solid obtained filtered off and dried.

Yield: 3.4 g. (32.1%)

EXAMPLE 9.

PREPARATION OF 5,6-DIMETHOXYPHTHALIDYL ESTER OF
PENICILLIN

Potassium-benzylpenicillin (2.73 g. 0.00734 mole) was stirred in dry dimethylformamide (100 ml) with 3-bromo-5,6-dimethoxyphthalide (2.0 g., 0.00734 mole) for 12 hours. The mixture was poured into iced water (1 l.) with vigorous stirring and the solid filtered, dried and crystallised from isopropanol.

Yield: 1.6 g. 41.5%

EXAMPLE 10.

6-METHOXY-PHTHALIDYL ESTER OF BENZYL PENICILLIN

Benzylpenicillin, potassium salt (3.59 gms; 0.00966M) and 3-bromo-6-methoxyphthalide (2.35 gms; 0.00966 M) were stirred overnight in dry dimethylformamide. The mixture was poured into water (1 l.) and stirred for $\frac{1}{2}$ hour. Solid sodium chloride was then added to the resulting emulsion and the solid filtered, washed well with water and dried.

Yield: 4.5 gms; 33.8%

Hydroxylamine Assay 110.5%

EXAMPLE 11.

3-PHENYLPHTHALIDYL PENYLACETAMIDOPENICILLANATE

Ethyl chloroformate (4.8 ml. 0.05M) and pyridine (10 drops) was added to a stirred solution of sodium phenylacetamidopenicillanate (18.5 g. 0.05M) in methylene dichloride (250 ml) at -10°C. After stirring for $\frac{1}{2}$ hour an almost clear solution was obtained to which a solution of 2-benzoylbenzoic acid (11.3 g. 0.05M) in methylene dichloride (100 ml) was added and the mixture stirred at ambient temperature for 3–4 hours. A fine white solid which precipitated during the course of the reaction was filtered off and the methylene dichloride removed in vacuo to leave a pale yellow foam which was dissolved in ethyl acetate (500 ml). Insoluble material was filtered off and the clear yellow filtrate was washed twice with 200 ml portions of 1N sodium bicarbonate and twice with 200 ml portions of a saturated brine solution.

After drying over anhydrous magnesium sulphate, the ethyl acetate layer was filtered and concentrated in vacuo to give a yellow foam, which was dissolved in diethyl ether (100 ml) and added dropwise with stirring to a solution of petroleum ether 40–60° (about 500 ml). The ester precipitated immediately as a pale yellow amorphous powder (6.8 g. 25.3%).

EXAMPLE 12.

3-METHYL PHTHALIDYL ESTER OF BENZYL PENICILLIN

Method

The potassium salt of benzylpenicillin (0.015 m) was dispersed in dry dimethylformamide (50 ml) and the mixture was chilled to 0°C. A constant stream of nitro-

gen was bubbled through the mixture and freshly prepared crude 3-chloro-3-methylphthalide (0.015 m) was added in one portion together with a catalytic quantity of sodium iodide. The reaction was maintained at 0°C for 15 minutes, allowed to warm to room temperature and then continued for a further 30 minutes. The whole mixture was then poured into ice-water and the white precipitate obtained was filtered, washed with water, dried in vacuo to yield the title ester.

Crude yield (containing benzylpenicillin as indicated by biochromatogram Rf 0.60) 65%.

Following further purification by chromatography on silica gel using ethyl acetate petroleum ether (60—80°) (4:1) as elutant and treatment with sodium bicarbonate solution, a product was obtained as an amorphous white solid from ether/petroleum ether (40—60°C).

EXAMPLE 13.

3-METHYL PHTHALIDE ESTER OF 6[D(-)- α -AMINOPHENYLACETAMIDO] PENICILLANIC ACID, HYDROCHLORIDE

Method

The 3,3-methyl phthalide ester of phenoxymethylpenicillin was cleaved by known methods using PCl_5 followed by treatment with methanol and hydrolysis to give the corresponding 6APA ester. The product was isolated as the para-toluene sulphonate salt.

The 6APA ester was then acylated using D(-)N-(1-methoxycarbonylpropen-2-yl)- α -amino-phenylacetate via the ethoxy formic mixed anhydride and isolated as the 6[D(-)- α -aminophenylacetamido] penicillanic acid hydrochloride salt following treatment with dilute hydrochloric acid.

EXAMPLE 14.

3-METHYL PHTHALIDE ESTER OF PHENOXYMETHYLPENICILLIN VIA THE MIXED ANHYDRIDE ROUTE

Method

The potassium salt of phenoxymethylpenicillin (11.64 g, 0.03m) was dispersed in dry methylene dichloride (200 mls) and the mixture chilled to -5°C. To the stirred suspension, ethyl chloroformate (3.24 g, 0.03m) was added dropwise together with a catalytic quantity of pyridine. The mixture was stirred at -5°C for 30 minutes.

o-Acetyl benzoic acid (4.92 gm, 0.03m) was dissolved in dry ethyl acetate (150 ml) and the solution was then added to the reaction mixture. The reaction was continued at ambient temperature for 18 hours.

The solvent was evaporated in vacuo to yield a mobile straw coloured syrup. The syrup was dissolved in ethyl acetate (250 ml) and washed successively with dilute bicarbonate solution (100 ml 0.25N) and water (100 mls) and then dried over anhydrous magnesium sulphate. The drying agent was filtered off and the solvent removed in vacuo to yield a foam.

T.l.c. and n.m.r. evidence showed the product to be the required ester contaminated to some small degree with unknown materials. The ester was therefore further purified by column chromatography, using silica gel and ethyl acetate, petroleum ether (60—80°C) (4:1 ratio v/v) as elutant. The appropriate eluted fractions were combined and the solvent evaporated in vacuo to yield a gum. An amorphous solid was obtained by firstly triturating the gum with anhydrous ether and then with an acetone, ether mixture and pouring the respective solutions into petroleum ether (40—60°).

Yield: 4.7g (31%)

EXAMPLE 15.

3-METHYL PHTHALIDYL ESTER OF PHENOXYMETHYLPENICILLIN VIA THE CORRESPONDING ESTER OF BENZENE SULPHONIC ACID

Method

o-Acetyl benzoic acid (4.92g, 0.03m) was dispersed in dry ethyl acetate (100 ml) and chilled to 0°C. Dry pyridine (2.37g, 0.03m) was then added to the stirred suspension followed by the dropwise addition of benzene sulphonyl chloride (5.31g, 0.03m). The mixture was allowed to stand for a protracted period at 4°C.

The reaction contents were warmed to ambient temperature and the potassium salt of phenoxymethylpenicillin (11.64g; 0.03m) was added with stirring. The reaction was then allowed to continue for a further 12 hours.

The mixture was filtered to yield a yellow filtrate and a solid residue; the latter was discarded. The filtrate was washed with dilute sodium bicarbonate solution (3 x 100 ml 2% w/v), water (2 x 100 ml) and brine and finally dried over anhydrous sodium sulphate. The solution was then filtered and the solvent evaporated in vacuo to yield a yellow syrup. The syrup was dissolved in the minimal quantity of acetone, diluted with ether and the solution was then poured into excess petroleum ether (40-60°C) affording an amorphous yellow solid. The product was filtered, washed with petroleum ether and dried in vacuo (Yield: 2.5g, 17%). The ester was characterised by n.m.r. and i.r. and displayed spectra identical to that of an authentic sample.

EXAMPLE 16.

(a) PREPARATION OF o-ACETYL PHENYL ACETIC ACID

Method

3-Methyl indene was prepared by dehydrating the carbinol, with acid, formed from the Grignard reaction of 1-indanone with methyl magnesium iodide o-Acetyl-phenyl acetic acid was prepared from 3-methyl indene by a dichromate oxidation in 58% yield.

(b) PREPARATION OF THE 1-METHYL-ISOCHROMAN-3-ONE ESTER OF PHENOXYMETHYLPENICILLIN

Method

To a stirred suspension of phenoxymethylpenicillin potassium salt (7.76g, 0.02M) in methylene dichloride (100ml) at -5°C was added pyridine (6 drops) and ethyl chloroformate (1.91 ml; 0.02M). The mixture was stirred at -5°C for ½ hour. A suspension of o-acetyl phenyl acetic acid (3.56g; 0.02M) in dry methylene dichloride (50ml) was added. The reaction mixture was stirred at -5°C for ½ hour and then allowed to warm to room temperature and stirred for a further 4 hours. The now almost clear solution was water washed, dried over magnesium sulphate, filtered and the solvent evaporated in vacuo to give a solid foam.

Yield 2.0g = 15.6%

EXAMPLE 17.

PERI-NAPHTHALIDYL ESTER OF PHENOXY-METHYL-PENICILLIN

Phenoxymethyl penicillin, potassium salt (15.52 gms, 0.04 mole) in dry methylene dichloride (200 ml) was cooled to -5°C and treated with ethyl chloroformate (4.34 gm; 3.82 ml; 0.04 mole) and pyridine (0.4 ml) and stirring continued for 1 hour at -5°C.

Peri-naphthaldehydic acid (200 ml) was added to the mixed anhydride solution and the mixture stirred for 4 hours at room temperature.

The mixture was filtered through Celite washed with N/2 sodium bicarbonate solution (100 ml), water (100 ml) and saturated brine (100 ml), and dried over anhydrous magnesium sulphate. The solution was evaporated in vacuo to low volume and poured into 40-60° petrol (3 l) with vigorous stirring. The solid was filtered, washed with petrol and dried.

Yield: 3.1 gms 14.6%

CHAPTER 18.

3-PHENYL PHTHALIDYL ESTER OF PHENOXYMETHYLPENICILLIN

The potassium salt of phenoxymethylpenicillin (7.76g, 0.02m) was dispersed in dry dimethyl formamide (75 ml) at ambient temperature. The acid chloride of o-benzoyl benzoic acid (4.9g, 0.02m) was added to the stirred suspension and the reaction was continued at room temperature for 4 hours.

The reaction mixture was then poured into ice-water (600 ml) and the brown precipitate which was obtained was extracted into chloroform (4 x 400 ml). The chloroform solution was washed successively with water (3 x 200 ml) diluted with sodium bicarbonate solution (2 x 200 ml 2% w/v), water (2 x 200 ml) and finally brine. The solution was then dried (Na₂SO₄), filtered and diluted with petroleum

ether (40—60°C). A small quantity of a flocculent precipitate was obtained which was filtered and discarded. The filtrate was dripped slowly into an excess of petroleum ether (40—60°C) to yield a brown amorphous solid.

Yield: 2.4g (21%)

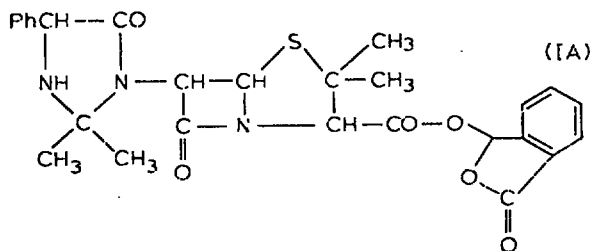
Biochromatographic evidence showed the product to be the required ester (Rf 0.95). T.l.c. data showed the product to contain a small quantity of the parent acid chloride intermediate; this latter result was also reflected in the n.m.r. data.

EXAMPLE 19.

PHTHALIDYL ESTER OF D- α -AZIDOBENZYL PENICILLIN

To a suspension of the sodium salt of azidocillin (6.64g) in 30 ml. of dimethylformamide was added at room temperature 3.10g. of 3-bromo-phthalide as a solution in 10 ml of dimethylformamide. The suspension was stirred over night at room temperature at the end of which a clear solution remained. This was poured into iced water, acidified and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate, brine, dried over Mg SO₄ and stripped to leave a yellow gum. 7.3 gm, 96% yield. An analytically pure sample could be obtained as a white sticky gum by chromatography on silica gel, and identified as the phthalidyl ester of [D] α -azidobenzylpenicillin. Hydroxylamine assay 105.1%.

EXAMPLE 20.



PHTHALIDYL ESTER OF HETACILLIN (1A)

Method

Hetacillin (2g, 0.0051 m) together with triethylamine (0.72 ml, 0.0051 m) were dispersed in dry dimethylformamide (25 ml) and the suspension was chilled to 0°C. To the stirred mixture, 3-bromophthalide (1.09g, 0.0051 m) was added in one portion. The cooling bath was then removed and the reaction allowed to warm to ambient temperature. The reaction was continued for 90 minutes.

The resulting mixture was then poured in ice water; the white precipitate obtained was filtered, washed extensively with water and finally freeze dried to yield a white amorphous solid.

Yield 1.33g 51%

Biochromatogram: Rf 0.85 (ester) together with trace amount of the parent penicillin Rf 0.33.

EXAMPLE 21.

PHTHALIDYL ESTER OF D, L β -AMINO- β -CYCLOHEX-3-ENYL ETHYL PENICILLIN

A solution of cyclohex-3-enecarboxaldehyde (55g., 0.5m), malonic acid (52g., 0.5m) and ammonium acetate (77g., 1.0m) in 95% ethanol in water (150 ml) was refluxed between 70—80°C for 24 hours. On cooling, a white solid precipitated out of the reaction mixture. This was collected, washed with acetone and desiccated over phosphorous pentoxide for 24 hours. The filtrate was reduced in volume and diluted with acetone resulting in a further batch of product being isolated.

Both crops were identified as D, L β -amino β -cyclohex-3-enyl propionic acid (m.p. 208—210°C, 60g., 70% yield).

The sodium salt of D, L β -amino β -cyclohexenyl propionate was prepared *in situ* by addition of the β -amino acid (16.9g., 0.1m) to a solution of sodium (2.3g 0.1m) in absolute ethanol (150 ml). Methyl acetoacetate (11.6g., 0.1m) was added

and the reaction mixture heated under reflux for 3 hours. The reaction mixture was filtered while still hot and, in cooling, white needles of the enamine derivative were obtained. These were collected, washed with ether and desiccated for at least 48 hours over anhydrous calcium chloride in a vacuum oven at 70°C. This gave sodium *D, L* β -amino (*N*-methoxy-carbonylpropen-2-yl) β -cyclohex-3-enyl propionate in quantitative yield (m.p. 1186--7°C). Ethyl chloroformate (0.74g; 5mM) and *N*-methyl morpholine (1 drop) was added to a suspension of sodium β -amino (*N*-methoxy-carbonylpropen-2-yl) β -cyclohex-3-enyl propionate (1.48g, 5 mM) in anhydrous acetone (40 ml) at -20°C. The reaction mixture was stirred for 20 minutes at -5° to 10°C yielding the mixed anhydride derivative.

p-Toluenesulphonate salt of phthalidyl 6-amino penicillinate (2.6g, 5mM) in anhydrous acetone (20 ml) was neutralised with triethylamine (0.7 ml) and cooled to -20°C. The mixed anhydride solution at 30°C was added and the resultant cloudy mixture stirred for an hour, its temperature being allowed to reach 20°C.

The acetone was removed *in vacuo* and the residue yellow gum was dissolved in 50% mixture of ethyl acetate and water (100 ml). This was adjusted to pH 1.5 with 5N hydrochloric acid and maintained at this pH for 30 minutes. The phases were separated and the yellow ethyl acetate layer washed with water (3 x 25 ml), saturated brine (50 ml) and filtered through a silicone treated filter paper. A light yellow gum was obtained on evaporation of the solvent *in vacuo*. This on trituration with anhydrous ether gave a light yellow solid — the phthalidyl ester of *D, L* β -amino β -cyclohex-3-enyl ethyl penicillin in 70% yield m.p. 120 (dec). Biochromatogram (*n* Butanol/ethanol) of the penicillin showed a single zone Rf. 0.95 and its purity by hydroxylamine assay 74.2%.

EXAMPLE 22.

PTHALIDYL ESTER OF *D*(-) α -GUANIDINO-*p*-HYDROXYBENZYL PENICILLIN HYDROCHLORIDE

A solution of *D*(-) α -guanidin-*p*-hydroxy-phenyl acetic acid hydrochloride (2.45 g., 0.01 M) in dimethylformamide (12 ml) was added to a stirred solution of phthalidyl-6-aminopenicillanate (3.48g., 0.01M) and dicyclohexylcarbodiimide (2.06 g., 0.01M) in dry methylene chloride (30 ml) over a period of 5 minutes. The reaction mixture was stirred in a cold water bath for 1½ hours, then in an ice-bath for 1 hour. The precipitate of dicyclohexylurea was filtered off, and the filtrate washed with N hydrochloric acid (2 x 30 ml) and brine (30 ml). The organic layer was separated, dried (MgSO₄) and added dropwise to a stirred dry ether (500 ml). The product (3.80 g., 66%) was filtered off washed with ether and dried *in vacuo*.

EXAMPLE 23.

PTHALIDYL ESTER OF *D, L* α -GUANIDINO-4-HYDROXY-3-METHYL- BENZYL PENICILLIN HYDROCHLORINE

The penicillin was prepared by dicyclohexylcarbodiimide coupling of *DL*- α -guanidino-4-hydroxy-3-methyl-phenylacetic acid hydrochloride (1.30g., 0.005 mole) in the manner described in Example 22. The yield of product was 1.40 g., (48%).

EXAMPLE 24.

PTHALIDYL ESTER OF *D, L*- α -GUANIDINO-4-HYDROXY-2- METHYLBENZYL PENICILLIN HYDROCHLORIDE

Following the procedure described in Example 22, *DL*- α -guanidino-4-hydroxy-2-methylphenylacetic acid hydrochloride (1.30 g., 0.005 mole) was coupled to the phthalidyl ester of 6-aminopenicillanic acid (1.74g., 0.005 mole) in the presence of dicyclohexylcarbodiimide. The yield of product was 1.20g. (41%).

EXAMPLE 25.

PTHALIDYL ESTER OF α -SULPHOBENZYL-PENICILLIN SODIUM SALT

Phthalidyl 6-aminopenicillanate (6.96 g., 0.02 mol) was dissolved in acetone (100 ml) cooled in an ice bath and treated with a 0.6M solution of α -sulphophenyl-acetylchloride in ether (35.5 ml.,) 0.02 mol). The solution was adjusted to pH 6.5 by the addition of *N* aqueous sodium hydroxide solution and stirred for 30 minutes. Phenylacetylchloride (2 ml) was added, the solution re-adjusted to pH 6.5 then

stirred for a further hour. The solvents were removed in vacuo and the residue diluted with water (100 ml). This aqueous solution was washed with ether (2 x 200 ml) and saturated with sodium chloride whereon an oil separated. The oil was collected and the aqueous phase extracted with ethyl acetate (2 x 100 ml). The oil and ethyl acetate extracts were combined, washed with saturated brine (100 ml) and evaporated to dryness to give a yellow solid (6.28g.). This solid was dissolved in water (200 ml) washed with ether (2 x 200 ml), filtered through Celite and the solution saturated with sodium chloride. The precipitated oil was extracted with n-butanol (200 ml) and washed with water (2 x 50 ml). Evaporation of the n-butanol solution yielded the phthalidyl ester of α -sulphobenzylpenicillin sodium salt (1.32g., 11.5%).

EXAMPLE 26.

(a) PHTHALIDYL ESTER OF α -(BENZYLOXYCARBONYL)BENZYL PENICILLIN

Phthalidyl ester of 6-aminopenicillanic acid from the p-toluene sulphonate salt (5g.) was dissolved in acetone (50 ml) cooled to 0° and treated with triethylamine (1.4ml). Monobenzylphenylmalonate (2.7g) was converted to the acid chloride by refluxing with thionyl chloride. Excess thionyl chloride was removed by evaporation under reduced pressure and the residue dissolved in dry acetone (20 ml). This solution was added to the 6-aminopenicillanic acid ester and stirred for 1 hour at 0°. Filtration of the reaction mixture followed by evaporation under reduced pressure gave a residue which was dissolved in ethyl acetate (100 ml) and filtered to clarify. The filtrate was washed with N sodium bicarbonate (10 ml) followed by water (30 ml), dried over anhydrous magnesium sulphate and evaporated to give an oil. Trituration of this oil with di-isopropyl ether followed by petroleum ether gave a yellow solid in 50% yield.

(b) PHTHALIDYL ESTER OF α -CARBOXYBENZYL PENICILLIN

Phthalidyl ester of α -(benzyloxycarbonyl)benzylpenicillin (2.9g) in methanol (100 ml) was added to a prehydrogenated mixture of 5% palladium on calcium carbonate (9g.) in ethanol (50 ml) and hydrogenation continued until no more hydrogen was absorbed. The mixture was filtered through Celite and evaporated to dryness. The residue was mixed with water (25 ml) and ethyl acetate (15 ml) and N sodium bicarbonate added to bring the pH to 7.0. The layers were separated and the aqueous phase was washed with ethyl acetate, acidified to pH 1.5 with N hydrochloric acid and extracted with ethyl acetate. Evaporation of the dried organic layer gave a yellow foam which after trituration with petroleum ether gave a yellow solid 0.7g (27%).

EXAMPLE 27.

PHTHALIDYL D(-)- α -AMINO-3-THIENYL-ACETAMIDOPENICILLANATE

A mixture of anhydrous D(-)- α -amino-3-thienylacetamidopenicillanic acid (11.83g. 0.033M) and triethylamine (4.73 ml. 0.033M) was stirred in acetone containing 1% of water (300 ml) at ambient temperature for $\frac{1}{2}$ hour. Potassium bicarbonate (3.5g) and 3-bromophthalide (7.10g. 0.033M) were added at this stage to the penicillin salt and the mixture was stirred at ambient temperature overnight. The triethylamine hydrobromide which precipitated during the course of the reaction was filtered off and the orange brown filtrate concentrated in vacuo to 50—75 ml and added to ethyl acetate (250 ml). The ethyl acetate layer was washed twice with 150 ml portions of 2% aqueous sodium bicarbonate and twice with 100 ml portions of water. The organic layer was mixed with water (200 ml) and the mixture vigorously stirred at pH 2.0—2.5 for 0.75 hour. The ester was salted out into the ethyl acetate layer by the addition of sodium chloride and the organic layer was separated and dried over anhydrous magnesium sulphate. After filtration the ethyl acetate was diluted with an equal volume of diethyl ether which precipitated the ester as a white amorphous hydrochloride salt in 42% yield, which was washed well with diethyl ether.

Hydroxylamine assay = 90.7%.

EXAMPLE 28.

PHTHALIDYL ESTER OF CLOXACILLIN (6-[3-0-CHLOROPHENYL-5-METHYL ISOXAZOLE-4-CARBAMIDO] PENICILLANIC ACID)

Sodium cloxacillin (14.3 g. 0.03M) was dispersed in dry dimethylformamide (400 mls). To the stirred mixture, 3-bromophthalide (6.39g. 0.03M) was added in one portion and the reaction was continued for 2 hours at ambient temperature.

The resulting mixture was then poured into ice water; the white precipitate obtained was filtered and washed extensively with water, and finally freeze dried to yield a white amorphous solid. (15.2 g. 89%). Biochromatographic evidence showed the product to be the desired ester (R_f 0.95).

A small sample of the product was further purified by dissolving in ethanol and pouring the solution into excess petroleum ether.

EXAMPLE 29.

PREPARATION OF PHTHALIDYL ESTER OF 6[D(-)- α -AMINO-(p-HYDROXYPHENYLACETAMIDO) PENICILLANIC ACID*Method*

A solution of phthalidyl 6-aminopenicillanic acid p-toluene-sulphonate (10.4g: 0.02M) in ethyl acetate (500 ml) was thoroughly shaken with 2% sodium bicarbonate solution (314 ml), and then with water (225 ml containing 7 ml of 2% sodium bicarbonate solution). The organic layer was dried over magnesium sulphate, filtered and the solvent evaporated off in vacuo to give a foam.

A suspension of enamine protected α -amino-p-hydroxyphenylacetic acid sodium salt (5.74g: 0.02M) in dry ethyl acetate (100 ml) was cooled to -15°C with stirring. N-methyl-morpholine (2.02 ml) and ethylchloroform at (3.81 ml: 0.02 M) were added, stirring was continued at 15°C for 6 minutes.

An ice-cold solution of the 6-amino-penicillanic acid ester in dry ethyl acetate (100 ml) was then added and the reaction mixture stirred at -12°C to -14°C for 10 minutes, and then at room temperature for $\frac{1}{2}$ hour.

The reaction mixture was washed with N/2 sodium bicarbonate solution (40 ml), water (2×20 ml) and then the organic layer was dried over magnesium sulphate. The magnesium sulphate was filtered off and the solvent removed in vacuo to give a yellow foam.

The foam was dissolved in acetone (80 ml) and water (80 ml). The solution was vigorously stirred and the pH adjusted to 2.5 with 5N hydrochloric acid. The acetone was evaporated off in vacuo and the aqueous extracted with ethyl acetate (80 ml). The organic layer was then diluted with petrol $40^\circ-60^\circ$ (70 ml) and extracted with water at pH 3 (100 ml).

The combined aqueous extracts were saturated with solid sodium chloride and the oily upper layer removed. The oil was dissolved in iso-propanol (50 ml) and filtered. The solution was then dripped into excess ether, and the resulting solid was then filtered off and dried.

Yield = 1.5 g = 14.0%

Hydroxylamine assay = 94.9%

EXAMPLE 30.

5,6-DIMETHOXYPHTHALIDYL D,L- α -AMINO-3-THIENYLMETHYL PENICILLANATE, HCl

D,L- α -amino-3-thienylmethylpenicillin (7.1 g. 0.02m) and triethylamine (2.02g. 2.8ml. 0.02m) were mixed with acetone (140 ml) containing 1% water. After stirring the suspension for $\frac{1}{2}$ hour potassium bicarbonate (2g. 0.02m) and 3-bromo-5,6-dimethoxyphthalide (5.46g. 0.02m) were added and the mixture stirred vigorously at room temperature for 4 hours.

The mixture was filtered through Celite and evaporated at room temperature to about 30 mls. Ethyl acetate (200 ml) was added and the solution washed with 2% sodium bicarbonate solution (2 times with 40 ml), water (40 ml) and then water (60 ml) was added to the ethyl acetate layer and, with vigorous stirring, the pH was maintained at 1.8 by dropwise addition of 5N hydrochloric acid. The organic layer was separated, dried over anhydrous magnesium sulphate and poured into stirring dry ether. The solid was filtered, washed and dried.

A further quantity of solid was obtained by salting the acidic aqueous phase and pouring a propanolic solution of the resultant oil into ether.

Yield: 2.5g (21.4%)

Hydroxylamine assay: 106.3%

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EXAMPLE 31.

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PHthalidyl 6-[(HEXAHYDRO-1H-AZEPIN-1-yl)-METHYLENEAMINO]-PENICILLANATE, HYDROCHLORIDE

N-formylhexamethyleneimine (6.35 g) was dissolved in dry diethyl ether (200 ml). Oxalyl chloride (4.25 ml) in dry diethyl ether (30 ml) was added dropwise to the ethereal solution of the imine and the mixture stirred at 0--5° for ½ hour and at ambient temperatures for 6 hours. The precipitated amide chloride was collected and washed well with dry ether and placed immediately in a dessicator containing P₂O₅.

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Phthalidyl 6-aminopenicillanate tosylate (11.44 g; 0.025 M) was suspended in ethyl acetate (650 ml) under continuous stirring and cooling in an ice-bath. A solution of ice-cold 2% sodium bicarbonate (450 ml) was added and the organic layer separated and shaken with ice-water (500 ml) containing 2% sodium bicarbonate (10 ml) and then dried over anhydrous magnesium sulphate. After filtration the solvent was evaporated *in vacuo* to yield the phthalidyl 6-aminopenicillanate as a foam. The foam was dissolved in chloroform (75 ml) and triethylamine (7.0 ml) was added at -30° to -40°C. The chlorohexamethyleneiminium chloride (4.8g; 0.025M) in chloroform (35 ml) was added dropwise at a temperature of ca. -20°C. After standing at -20°C for ½ hour the temperature was raised to 0° within ½ hour.

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The solution was evaporated to dryness *in vacuo* and the residue stirred with diethyl ether (300 ml). Undissolved triethylamine hydrochloride was filtered off and the solvent again evaporated *in vacuo* and the residue dissolved in isopropanol (25 ml). The solution was cooled to 0°C with stirring and a solution of 8.5 N hydrogen chloride in isopropanol (2.5 ml) was added. The product precipitated in 46% yield and was washed well with dry diethyl ether. The product was re-precipitated from methanol-diisopropyl ether with an 85% recovery.

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Hydroxylamine assay = 74.9%

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EXAMPLE 32.

(a) PREPARATION OF CHLORODIMETHYLFORMIMINIUM CHLORIDE

Method

Oxalyl chloride (6.35g; 0.05 M) dissolved in dry ether (50 ml) was slowly added to a solution of dimethylformamide (3.65g; 0.05 M) at 0°C. The precipitate formed was filtered almost immediately and washed with dry ether. The solid was used immediately for the reaction below.

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(b) PREPARATION OF PHthalidyl 6-(N,N-DIMETHYL-FORMAMIDINE-N'-)-PENICILLINATE HYDROCHLORIDE

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Method

A solution of phthalidyl 6-aminopenicillanic acid p-toluene-sulphonate salt (10.40 g; 0.02M) in ethyl acetate (500 ml) was thoroughly washed with 2% sodium bicarbonate solution (314 ml) and water (250 ml) containing 7 ml. of 2% sodium bicarbonate solution. Dried over magnesium sulphate, filtered and the solvent removed *in vacuo* to give a foam.

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The foam was dissolved in chloroform (75 ml) and to it was added triethylamine (6.1 ml) at -30° to -40°C. To the stirred solution was added chlorodimethylformiminium chloride (2.56 g; 0.02M) in chloroform (40 ml). The temperature was allowed to rise to 0°C within 1 hour. The solution was then evaporated to dryness *in vacuo* and the residue treated with ether (300 ml) and filtered. The ether was evaporated off *in vacuo* and the gum dissolved in isopropyl alcohol (20 ml). The solution was cooled to 0°C. with stirring and 8.5N hydrogen chloride in isopropyl alcohol (2 ml) was added. A solid was precipitated out with ether.

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Yield = 1.6 g = 18.2%

EXAMPLE 33.

 α,β -BIS PHTHALIDYL ESTER CARBENICILLIN (α -CARBOXY-PHENYLACETAMIDO PENICILLANIC ACID)

The disodium salt of carbenicillin (6.33g; 0.015M) was dispersed in dimethylformamide (100 ml) at 0°C. 3-Bromophthalide (6.39g; 0.03M) was added in one portion to the stirred suspension and allowed to react for a further $\frac{1}{2}$ hour at 0° and then for a period of 2 hours at ambient temperature.

The reaction mixture was poured into ice-cold water (1000 ml) and the diester which precipitated out of the aqueous solution extracted into ethyl acetate (250 ml) and washed with 2% sodium bicarbonate (2 x 250 ml) and water (2 x 250 ml) and then dried over anhydrous magnesium sulphate. After filtration the ethyl acetate was concentrated in vacuo to ca 75 ml. and diethyl ether (100 ml) was slowly added to the stirred ethyl acetate solution to precipitate the diphtalidyl ester as a white amorphous solid in 85% yield.

Recrystallisation from ethanol gave the product as a white crystalline solid in 69% yield.

EXAMPLE 34.

 α,β -BISPHTHALIDYL ESTER OF 6[D- α -CARBOXY-3-THIENYL-ACETAMIDO] PENICILLANIC ACID

The disodium salt of D- α -carboxy-3-thienylacetamido penicillanic acid (8.3g; 0.02M) was dispersed in dry dimethylformamide (100 ml) at 0°C. 3-Bromophthalide (8.52g; 0.04M) was added in one portion to the stirred suspension and allowed to react for a further $\frac{1}{2}$ hour at 0° and then for a period of 2 hours at ambient temperatures.

The reaction mixture was poured into ice-cold water (1000 ml) and the solid which precipitated immediately out of the aqueous solution was extracted into ethyl acetate (250 ml) and washed with 2% sodium bicarbonate (2 x 250 ml) and water (2 x 250 ml) and then dried over anhydrous magnesium sulphate. After filtration the ethyl acetate was concentrated in vacuo to ca 70 ml. and diethyl ether (100 ml) was slowly added to the stirred ethyl acetate solution to precipitate the diphtalidyl ester as a white amorphous solid in 90% yield. Recrystallisation from ethanol gave the product as a white crystalline solid in 70% yield.

EXAMPLE 35.

COMBINED SALT OF 6-[3-(2 CHLORO-6-FLUOROPHENYL)-5-METHYL ISOXAZOLE-4-CARBAMIDO] PENICILLANIC ACID (FLUCLOXACILLIN) AND PHTHALIDYL D(-)- α -AMINO-PHENYL ACETAMIDOPENICILLANATE

A solution of the sodium salt of flucloxacillin (4.76g; 0.01M) in water (100 ml) was mixed with a solution of phthalidyl D(-)- α -aminophenylacetamidopenicillanate, hydrochloride in water (150 ml) at ambient temperatures. Immediately a white amorphous solid precipitated which was collected, washed well with cold water and dried over P₂O₅ in vacuo to give an 85% yield of the combination salt.

EXAMPLE 36.

SALT OF FLUCLOXACILLIN AND PHTHALIDYL 6-[(HEXAHYDRO-1H-AZEPIN-1-yl)METHYLENEAMINO]-PENICILLANATE

A 10% aqueous solution of the sodium salt of flucloxacillin (4.76 g; 0.01M) and a 10% aqueous solution of phthalidyl 6-[(hexahydro-1H-azepin-1-yl)methyleneamino] penicillanate, hydrochloride (4.93g; 0.01M) were mixed at ambient temperatures. Immediately a white amorphous solid precipitated which was collected, washed well with cold water and dried over P₂O₅ in vacuo to give a 67% yield of the combination salt.

EXAMPLE 37.

PHTHALIDYL 7-(2-THIENYLACETAMIDO)CEPHALO-SPORANATE (cephalothin ester)

3-Bromophthalide (5.37g; 0.025M) was added to a stirred suspension of 7-(2-thienylacetamido)cephalosporanate (10.45g; 0.025M) in dimethylformamide (75

ml) at 0° and the mixture reacted for $\frac{1}{2}$ hour at 0°C and then for a further 1 hour at ambient temperatures, by which time a clear brown solution had formed. The reaction solution was added to ice cold water (ca. 1500 ml) and stirred for 20 minutes and the creamy/white solid which precipitated collected and washed well with cold water and then freeze dried to give 10.5 g. of an amorphous powder. Biochromatogram indicated two spots one major at $R_f = 0.90$ (ester) and a minor zone at $R_f = 0.39$ (unreacted cephalothin).

Hydroxylamine assay = 73.6%

The unreacted cephalothin was removed from the solid by dissolving it in the minimum amount of ethyl acetate and washing twice with 2% sodium bicarbonate and water. The organic layer was dried over magnesium sulphate (anhydrous) and the solvent evaporated in vacuo to yield a sticky solid which solidified upon trituration with a mixture of diethyl ether and petroleum ether, b.p. 40--60°. Yield 65%. The n.m.r. spectrum indicated that the major component was the Δ^3 isomer with approximately 10--20% of the Δ^2 isomer. A purer sample was obtained by recrystallisation from isopropanol, although the recovery was only 50%.

Hydroxylamine assay = 74.1%.

EXAMPLE 38.

PREPARATION OF 2-THIOPHTHALIDYL ESTER OF BENZYL PENICILLIN

Method

A suspension of sodium salt of benzylpenicillin (7.12g; 0.02M) was stirred in dry D.M.F. (50 ml) at 0°C. To this was added, in one portion, 3-bromo-2-thiophthalide (4.58g; 0.02M) in dry D.M.F. (20 ml). The reaction mixture was allowed to warm to room temperature and stirred for a further 2 hours. After this time it was poured into 2 litres of ice-water. The aqueous was then extracted with chloroform (3 x 200 ml). The chloroform extracts were combined, dried over magnesium sulphate, filtered and the solvent removed in vacuo. The gum was taken up in methanol (100 ml) and treated with charcoal. The solution was filtered and the solvent evaporated off in vacuo. The pale yellow gum was triturated with petrol 40°--60° and a solid obtained, which was filtered off and dried.

Yield = 1.3g = 13.3%

EXAMPLE 39.

Representative compounds made by the preceding Examples were subjected to an experiment to determine their hydrolysis characteristics under various conditions. The results are tabulated below.

TABLE I
Esters of 6[D(-) α -Aminophenylacetamido]Penicillanic Acid
Percentage Hydrolysis to 6[D(-) α -Aminophenylacetamido]Penicillanic Acid

Product of Example	Acid (pH 2.0) After (mins)						Aqueous Buffer (pH 7.0) After (mins)						Human Blood (pH 7.9) After (mins)					
	3			8			15			25			3			8		
	3	8	15	3	8	15	3	8	15	3	8	15	3	8	15	3	8	15
7	0	0	0	0	0	0	10	15	20	25	25	25	48	62	80	82	82	82
1	0	0	0	0	0	0	0	12	20	34	34	34	44	46	62	66	66	66
2	0	0	0	0	0	0	0	0	18	36	36	36	82	88	90	100	100	100
4	0	0	0	0	0	0	0	0	0	12	12	12	36	58	66	72	72	72
3	0	0	0	0	0	0	25	28	4.8	50	50	50	66	70	76	80	80	80
5	0	0	10	14	10	14	0	10	12	18	18	18	28	30	48	52	52	52

TABLE 2

Esters of Benzylpenicillin

Percentage Hydrolysis to Benzylpenicillin at 37°C in

Product of Example	Aqueous Buffer (pH 7.0) After (mins)				Human Blood (pH 7.0) After (mins)			
	3	8	15	25	3	8	15	25
12	0	0	0	0	0	0	16	40
9	0	0	0	0	74	68	66	62
38	0	0	0	0	22	32	38	38
10	0	0	12	22	60	63	78	84
11	0	10	16	28	18	46	52	60

TABLE 3

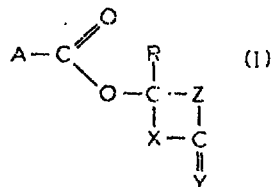
Esters of Phenoxymethylpenicillin

Percentage Hydrolysis to Phenoxymethylpenicillin



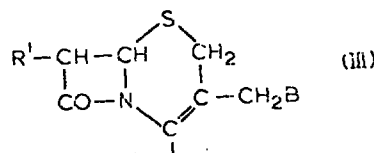
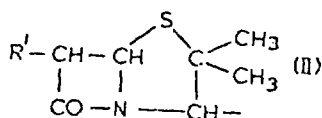
WHAT WE CLAIM IS:—

1. Compounds of formula (I) and pharmaceutically acceptable acid-addition salts of those compounds of formula (I) which contain a basic nitrogen atom:—

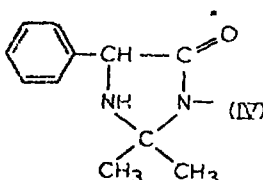


wherein X and Y are the same or different and each represents oxygen or sulphur;
Z represents a straight or branched, saturated or unsaturated divalent hydrocarbon radical, having from 1 to 7 carbon atoms, in which any two adjacent carbon atoms are joined in a carbocyclic ring system which may carry one or more substituents;
R represents hydrogen or an alkyl, alkenyl, alkynyl, aryl or aralkyl group, or a functional substituent;

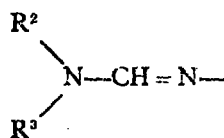
A represents a group of formula (II) or (III):—



wherein B represents hydrogen or an acetoxy group and R¹ is an organic acylamino group, a group of formula IV:—



or a group of formula (V):—



wherein R¹ and R² each represent a C₁₋₇ alkyl group, or R¹ and R² taken together with the nitrogen atom to which they are attached form a monocyclic ring, the foregoing definition of compounds of formula (I) being subject to the proviso that when A is a group of formula (II) R¹ is not the D(-)- α -aminophenylacetanido group when R is hydrogen, X and Y are both oxygen and Z is a 1,2-phenylene group.

2. Compounds as claimed in claim 1 wherein X and Y in formula (I) are both oxygen, and pharmaceutically acceptable salts of those compounds.

3. Compounds as claimed in claim 1 or claim 2 wherein group R¹ is an organic acylamino group.

4. Compounds as claimed in claim 3 wherein the group R¹ is phenylacetamido, 2-, or 3- thienylacetamido, phenoxyacetamido, α -aminophenylacetamido, α -guanidino-*para*-hydroxyphenylacetamido, α -carboxyphenylacetamido, α -sulphophenylacetamido, α -azidophenylacetamido, α -amino-2-(or 3-) thienylacetamido or *p*-hydroxy- α -aminophenylacetamido.

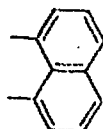


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5. Compounds as claimed in any one of the preceding claims wherein Z in formula (I) is a 1,2-phenylene group which may carry one or more substituents in the phenyl ring.

6. Compounds as claimed in any one of claims 1 to 4 wherein Z in formula (I) is a group of formula



7. Compounds as claimed in any one of the preceding claims wherein the group R in formula (I) is a methyl or phenyl group.

8. 5,6-Dimethoxyphthalidyl 6[D(-)- α -amino-phenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

9. 6-Methoxyphthalidyl 6[D(-)- α -aminophenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

10. 6-Chlorophthalidyl 6[D(-)- α -aminophenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

11. 4,5,6-Trimethoxyphthalidyl 6[D(-)- α -amino phenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

12. 6-Bromophthalidyl 6[D(-)- α -aminophenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

13. *Peri*-naphthalidyl 6[D(-)- α -aminophenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

14. 2-Thiophthalidyl 6[D(-)- α -aminophenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

15. 3-Methylphthalidyl 6[D(-)- α -aminophenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

16. Phthalidyl 6[D(-)- α -amino-3-thienylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

17. 5,6-Dimethoxyphthalidyl 6[D,L- α -amino-3-thienylacetamido] penicillanate and pharmaceutically acceptable addition salts thereof.

18. 6-Nitrophthalidyl 6[phenylacetamido] penicillanate.

19. 5,6-Dimethoxyphthalidyl 6[phenylacetamido] penicillanate.

20. 6-Methoxyphthalidyl 6[phenylacetamido] penicillanate.

21. 3-phenylphthalidyl 6[phenylacetamido] penicillanate.

22. 3-Methylphthalidyl 6[phenylacetamido] penicillanate.

23. 2-Thiophthalidyl 6[(phenylacetamido)penicillanate.

24. 3-Methylphthalidyl 6[phenoxyacetamido] penicillanate.

25. 1-Methyl-isochroman-3-one-1-yl 6[phenoxyacetamido] penicillanate.

26. *Peri*-naphthalidyl 6[phenoxyacetamido] penicillanate.

27. 3-phenylphthalidyl 6[phenoxyacetamido] penicillanate.

28. Phthalidyl 6[D(-)- α -guanidino-*p*-hydroxyphenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

29. Phthalidyl 6[α -guanidino-4-hydroxy-3-methyl-phenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

30. Phthalidyl 6[α -guanidino-4-hydroxy-2-methyl-phenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

31. Phthalidyl 6[α -sulpho-phenylacetamido] penicillanate and pharmaceutically acceptable salts thereof.

32. Phthalidyl 6[α -carboxy-phenylacetamido] penicillanate and pharmaceutically acceptable salts thereof.

33. α,β -Bisphthalidyl 6[α -carboxy-phenylacetamido] penicillanate.

34. α,β -Bisphthalidyl 6[α -carboxy-3-thienylacetamido] penicillanate.

35. Phthalidyl 6[α -azido-phenylacetamido] penicillanate.

36. Phthalidyl 6[β -amino- β -cyclohex-3-enylpropionamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.

37. Phthalidyl 6[-(3-*o*-chlorophenyl-5-methylisoxazole-4-carbamido] penicillanate.

38. Phthalidyl 6[D(-)- α -amino(*p*-hydroxy-phenylacetamido] penicillanate and pharmaceutically acceptable acid addition salts thereof.



39. Phthalidyl 6[(hexahydro-1H-azepin-1-yl)-methyl-encamino] penicillanate and pharmaceutically acceptable acid addition salts thereof.

40. Phthalidyl 6-(N,N-dimethylformamidine-N'-) penicillanate and pharmaceutically acceptable acid addition salts thereof.

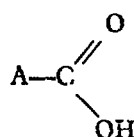
5 41. Phthalidyl 7-(2-alkenylacetamido) cephalosporanate.

42. The combination salt of 6[3-(2-chloro-6-fluoro-phenyl)-5-methyl isoxazole-4-carbamido] penicillanic acid and phthalidyl 6[D(-)-α-amino-phenylacetamido] penicillanate.

10 43. The combination salt of 6[3-(2-chloro-6-fluorophenyl)-5-methyl isoxazole-4-carbamido] penicillanic acid and phthalidyl 6[(hexahydro-1H-azepin-1-yl) methyl-encamino] penicillanate.

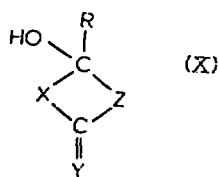
44. Phthalidyl 6[2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl] penicillanate.

15 45. A process for the preparation of compounds as claimed in claim 1 which process comprises
(a) reacting a compound of formula (IX)



(IX)

or a reactive esterifying derivative thereof, in which formula A is as defined in claim 1, with a compound of formula (X):--

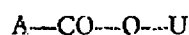


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or a reactive esterifying derivative thereof, in which formula X, Y, and Z and R are as defined in claim 1.

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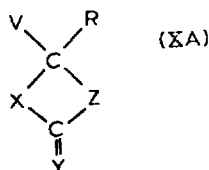
46. A process as claimed in claim 45 wherein a compound of formula (IXA)



(IXA)

wherein A is as defined in claim 1 is reacted with a compound of formula (XA)

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wherein R, X, Y and Z are as defined in claim 1 under conditions which cause the elimination of the elements of the compound UV with the consequent formation of the desired ester; the symbols U and V in formulae (IXA) and (XA) being such that U represents hydrogen or a salt-forming ion and V represents a hydroxy group, an alkylsulphonyloxy group or a halogen atom or U represents an organic acyl group and V represents a hydroxy group.

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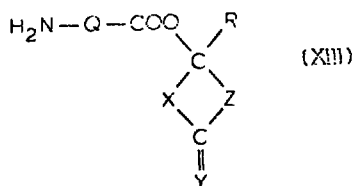
47. A process for the preparation of a compound as claimed in claim 1 wherein the group R¹ in radical A is an acylamino group which process comprises reacting a compound of formula (XIII):

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* C L M S *

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or a silyl derivative thereof wherein $\text{H}_2\text{NQ}-$ represents a 6-amino-penam-3-radical, 7-amino-3-methyl-ceph-3-em-4-radical or 7-amino-3-acetoxymethyl-ceph-3-em-4 radical and R, X, Y and Z are as defined in formula (I) with a reactive N-acylating derivative of a compound of formula (XIV)

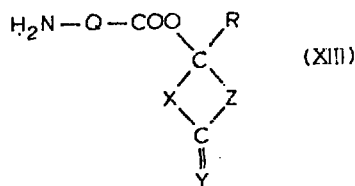


wherein R_1 is an organic acyl group which may carry a protected amino group, removing the silyl group, if present, by hydrolysis or alcoholysis, and, if a protected amino group is present, optionally converting it to a free amino group under acid or neutral conditions.

48. A process as claimed in claim 47 wherein the reactive N-acylating derivative compound (XIV) is the acid halide or mixed anhydride.

49. A compound as claimed in claim 1 whenever made by a process as claimed in any one of claims 45 to 48.

50. A chemical intermediate of formula (XIII)



wherein $\text{H}_2\text{NQ}-$ represents a 6-aminopenam-3-radical, a 7-amino-3-methyl-ceph-3-em-4 radical or a 7-amino-3-acetoxymethylceph-3-em-4 radical and R, X, Y and Z are as defined in claim 1, provided that when $\text{H}_2\text{NQ}-$ is a 6-aminopenam-3-radical and X and Y are both oxygen and R is hydrogen, Z is not a 1,2-phenylene radical.

51. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 44 and 49 together with a pharmaceutically acceptable carrier.

52. A pharmaceutical composition as claimed in claim 51 in a form suitable for oral administration.

R. SMITHER,
Chartered Patent Agent,
Agent for the Applicants.

PATENTS ACT 1949

SPECIFICATION NO 1377817

The following amendments were allowed under Section 29 on 12 August 1975

Page 1, line 15, page 24, line 7, *delete* 1 to 7 *insert* 2 to 7

Page 24, line 28, *delete* α - guanidino -

Page 24, *delete* lines 29, 30 and 31 *insert* α - carboxyphenylacetamido, or α - amino - 2 - (or 3-) thienylacetamido.

Page 25, line 1, *delete* any one of the preceding claims *insert* claim 3 or claim 4.