

PATENT SPECIFICATION

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(54) PENICILLIN PREPARATION

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, and having a place of business at 685 Third Avenue, New York City 17, New York, United States of America, 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 the production of (a) novel acylated organosilane derivatives of 6-aminopenicillanic acid, (b) novel organosilane derivatives of 6-aminopenicillanic acid which can be acylated and (c) the optional hydrolysis or alcoholysis of the acylated derivatives to give the corresponding penicillins known to have useful antibiotic activity.

Silylated derivatives of 6-aminopenicillanic acid and the use thereof in the preparation of semi-synthetic penicillins having antibiotic activity are known to the art. For example, mono- and disilylation of 6-aminopenicillanic acid for preparing intermediates which are readily acylated and then hydrolysed or alcoholysed to the corresponding penicillins having valuable antibiotic activities have been suggested and/or utilised. Thus, there is disclosed, by Glombitza in *Annalen* 673, 166 (1964), and in the patent literature; e.g. in U.S.A. Patent Specification No. 3,249,622 and British Patent Specification Nos. 959,853 and 1,008,468, the preparation of mono- and disilylated derivatives of 6-aminopenicillanic acid (6-APA), by employing, as silylating agents, monochlorosilanes, aminosilanes, and disilylamines, (such as trimethylchlorosilane, trimethylsilyldiethylamine and hexamethyldisilazane).

In none of the prior art exemplified by the noted publication and patents is there any suggestion of the possibility of employing a monohydrocarbyl dihalosilane or employing a trihalosilane (for example methylchlorosilane or methyltrichlorosilane) for the preparation of organosilane derivatives of 6-aminopenicillanic acid. This is no doubt because the resulting organosilane derivatives of 6-aminopenicillanic acid would be expected to contain reactive Si—Cl or Si—H groups which would interfere with subsequent acylation, or would be polymeric mixtures which are insoluble in solvents and would resist acylation.

We have now unexpectedly found that the reaction products of 6-APA and dihydrocarbyl dihalosilanes (e.g. dimethyldichlorosilane, methylphenyldichlorosilane and diphenyldichlorosilane) can be acylated with functional derivatives of α -aminoacids. The discovery has also been made that, not only are trihalosilanes as well as monohydrocarbyldihalosilanes in fact useable for preparing solvent soluble organosilane derivatives of 6-APA which can be acylated and the acylated products subjected to hydrolysis or alcoholysis to give penicillins but, moreover, they result in excellent yields and purity of the final penicillin products.

The well-known "silylated" derivatives of 6-aminopenicillanic acid are by definition tri-organo substituted (e.g. trimethylsilyl-) derivatives of 6-APA, as to avoid confusion we designate the products of 6-APA or a salt thereof and a trihalosilane or a dihalosilane as "silenated derivatives".

The present invention provides a process for the preparation of novel organosilane penicillins of the general formula:

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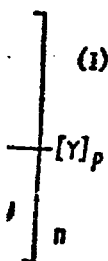
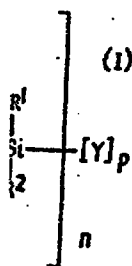
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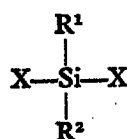


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atom. Some of these compounds, and the corresponding ones in which W is hydrogen, n is 1 and Y is of formula (III) are novel compounds and the invention also provides these novel compounds as intermediates. Thus the invention further provides compounds of the above general formula (I), in which R¹, R², W, m, n, p and Y have the meanings defined above, R³ is hydrogen and the following provisos apply:

- (a) when m is 0, p is 0, n is more than 1 and the two free valencies are joined together to complete a cyclic compound;
- (b) when n is more than 1, the moieties A of the additional groups B occur in random head-towards-head, head-towards-tail and tail-towards-tail disposition;
- (c) m is always equal to p;
- (d) when R¹ is alkyl, aryl or aralkyl, R² is halogen.

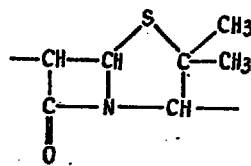
The silenated 6-aminopenicillanic acid starting material of formula (I), wherein R³ is hydrogen, can be prepared by reaction of 6-aminopenicillanic acid, or a salt thereof, with a di- or tri-halosilane of the following formula:



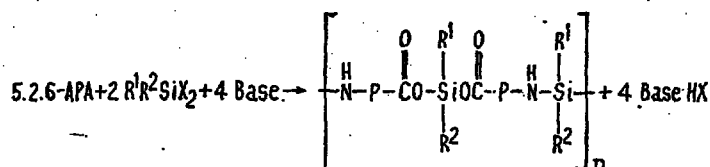
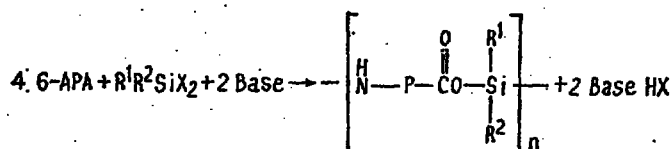
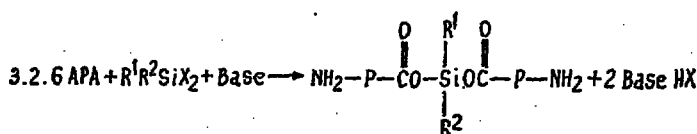
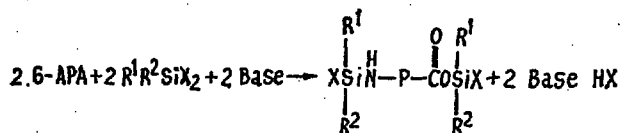
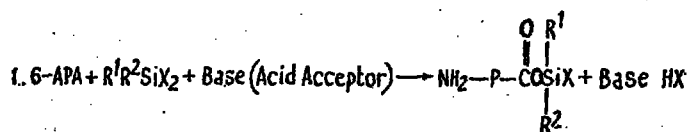
(IV)

wherein R¹, R² and X have the same meanings as in formula (I) above. To get the maximum yield, the reaction can be continued until formation of the salt of the respective hydrogen halide is substantially complete or until substantially all 6-aminopenicillanic acid has reacted. Preferably the 6-APA or salt thereof and compound of formula (IV) are heated in the presence of an acid acceptor. Preferably the reaction is carried out in solution. Suitable di- or tri-halosilanes which can be used include dimethyldichlorosilane, methylpropyldichlorosilane, dimethyldibromosilane, dibutyldichlorosilane, diphenyldichlorosilane, methylphenyldichlorosilane, dibenzyl dichlorosilane, ethylbenzyldibromosilane, methyldichlorosilane and methyltrichlorosilane.

Various proportions of di- and tri-halosilanes and acid acceptors can be employed for reaction with 6-APA to give various novel silenated products which contain a half to two silicon groups per APA group, and in which one or two of the halogen atoms of the di- or tri-halosilane have reacted. For example, the following reactions, wherein P=



are believed to occur, depending on the ratios of reactants used:



The products containing more than one "P" unit (i.e. wherein $n \geq 1$ in the foregoing formulae) are considered to be linear or cyclic dimers, trimers or higher polymers. In such cases, the repeating 6-APA moieties of the group units may be randomly disposed head-toward-tail, head-toward-head and/or tail-toward-tail in a given compound, as will be understood by those skilled in the art and referred to hereinbefore.

Although the silenated compounds have been prepared successfully using one-half to two moles of halosilane per mole of 6-APA, it is preferred for maximum efficiency to use approximately equimolar proportions. Suitable acid acceptors include ammonia, organic amines, alkali metal carbonates and alkaline earth metal carbonates. In general, it is preferred to use about two moles of an acid acceptor such as anhydrous ammonia or an amine, such as triethylamine or diethylamine, per mole of halosilane.

A wide range of anhydrous non-hydroxylic organic solvents are suitable as solvents for the silenation of 6-APA, including hydrocarbons (such as benzene and toluene) chlorinated solvents (such as methylene chloride, chloroform, ethylene dichloride and chlorobenzene) ethers (such as diethyl ether, dioxane and tetrahydrofuran) and other conventional solvents (such as methylisobutylketone, dimethylformamide, ethyl acetate and acetonitrile).

Among these solvents, methylene chloride, chloroform, acetonitrile and ethyl acetate are particularly useful. Since the halosilanes and the silenated products are decomposed by moisture and other hydroxylic agents, solvents employed as reaction media must be substantially anhydrous and free from alcoholic impurities. Although more than 30 ml. of solvent per g. of APA has been used successfully for the solenation reaction, the use of 10 ml. per g. is usually sufficient. In some instances, however, the use of high dilution will favour intramolecular reaction and silenated derivatives

of lower molecular weight, while a high concentration of reactants will favour inter-molecular reaction and higher molecular weight products.

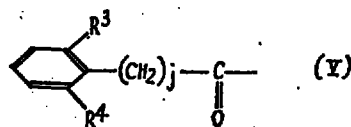
The reaction between 6-APA and a di- or tri-halosilane is carried out preferably at a temperature at which the reaction proceeds to completion in a reasonably short time, for example, between 10°C. and the boiling point of the solvent media. In refluxing methylene chloride, for example, the reaction of one mole of APA with one mole of dimethyldichlorosilane in the presence of two moles of triethylamine is complete in three hours, whereas after only one hour, about 4% of the APA remains unreacted. Complete solubility of the 6-APA used as a starting material and a quantitative yield of triethylamine hydrochloride are indicative of complete reaction.

The silylated 6-APA derivatives prepared as described above can be isolated by removing the base hydrohalide by filtration and distillation of the solvent, or if these intermediates are to be converted at once to a penicillin, the reaction mixture can be acylated directly without filtration or concentration. The silylated derivatives of 6-APA are readily soluble in a wide selection of anhydrous, non-hydroxylic solvents such as methylene chloride, chloroform, carbon tetrachloride, ethyl acetate, tetrahydrofuran, dioxane, benzene, toluene, dimethylsulfoxide, dimethylacetamide, dimethylformamide, acetonitrile, acetone, and methylisobutylketone, but are largely insoluble in hexane and cyclohexane. The β -lactam ring of the silylated derivatives is shown to be intact by infrared analysis as well as by the recovery of high purity 6-APA on treatment with water or an alcohol. For silylated products obtained using the reaction proportions given in Reactions 4 and 5 above using dimethyldichlorosilane nuclear magnetic resonance studies and elemental analyses indicate a 1:1 ratio of Si to 6-APA nucleus and absence of halogen, which is consistent with the structures shown for the products of these reactions.

The new organosilane penicillins of formula I wherein R^a is an acyl group, which are provided by the process of the invention are prepared by reaction of the silylated 6-APA intermediates with a suitable reactive derivative, (preferably a halide or anhydride, e.g. an N-carboxyanhydride) of an organic carboxylic acid in the presence of an acid acceptor. Suitable acylating agents include carboxylic acid halides, carboxylic acid anhydrides, mixed anhydrides with other carboxylic or inorganic acids, esters such as thiol esters and phenolic esters, lactones, and carboxylic acid with carbodiimides or N,N'-carbonyldiimidazoles. For the preparation of aminopenicillins, amino acid chloride hydrochlorides and amino acid N-carboxyanhydrides are suitable for acylating the APA derivatives.

Preferred organosilane penicillins of general formula (I) are those where R^a has one of the following formulae:

(i)



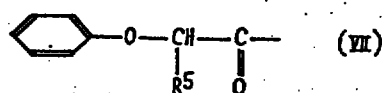
(wherein R^3 and R^4 are hydrogen or lower alkoxy and i is 0 or 1);

(ii)



(wherein R^3 has the same meaning as in formula V. above and preferably is an ethoxy radical)

(iii)



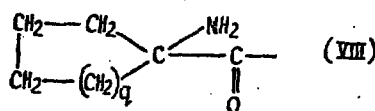
(wherein R^5 is hydrogen, lower alkyl or phenyl);

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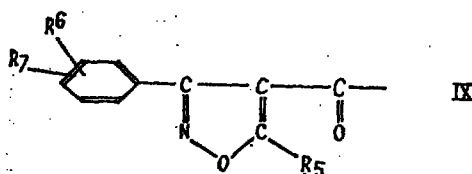
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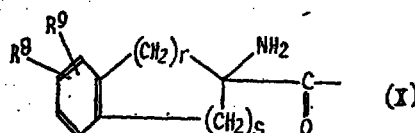
(wherein q is an integer from 1 to 5 and preferably is 2);

(v)



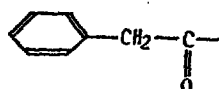
(wherein R^3 has the same meaning as in formula VII above, and R^6 and R^7 are hydrogen or halogen, R^5 in this formula preferably being methyl and R^6 and R^7 preferably being chlorine in the 2- and 6-positions);

(vi)

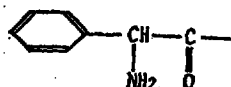


(wherein R^8 and R^9 are hydrogen, lower alkyl, lower alkoxy, phenyl or phenoxy; r is 0 or 1, and s is an integer from 1 to 3, with the provisos that when r is 0, s is greater than 1, and when r is 1, s is less than 3. Preferably, R^8 and R^9 are both hydrogen and r and s are both equal to 1);

(vii)



and (viii)



(XI)

Illustrative of some of the specific preferred acylating agents which may be used are the following: phenoxyacetyl chloride, 2,6-dimethoxybenzoyl chloride, benzenesulphonyl chloride 2-phenoxypropionyl chloride, 2-phenoxybutyryl chloride, D(-)-phenylglycyl chloride HCl, 1-aminocyclopentanecarboxylic acid chloride HCl, 2-aminocyclohexanecarboxylic acid chloride HCl, 2-amino-2-carboxyindane acid chloride HCl, 2-ethoxynaphthoyl bromide and 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carbonyl chloride.

The acylation reaction preferably is carried out in the presence of an acid acceptor which may be the same as or different from the one employed in preparing the silylated intermediate. For example, although a tertiary amine such as triethylamine is suitable for both reactions, the use of a weaker base such as N,N-dimethylaniline, pyridine, or quinoline, for the acylation reaction often affords higher yields. In the preparation of α -amino penicillins acylation with α -amino acid halide hydrohalides is best carried out in the absence of any strong base such as the alkyl amines. In fact, it is preferred to inactivate any excess strong amine, if present, by addition of a mineral acid salt of a weak amine. For example, using one mole of dimethyl-

dichlorosilane and an excess (e.g. 2.3 moles) of triethylamine in the silylation of one mole of 6-aminopenicillanic acid, the addition of 0.4 equivalent of dimethylaniline .2HCl prior to acylation with phenylglycol chloride HCl increased the overall yield of anhydrous ampicillin from 70 to 83% of theory.

In general, the same type of solvents are useful for the acylation of the silylated 6-APA products as for their original preparation. The silylated penicillins of the present invention are readily hydrolyzed or alcoholysed by treating with water or other hydroxyl-containing compound, e.g. an alcohol such as methyl or ethyl alcohol, to form the corresponding penicillins, many of which are useful pharmaceutical compounds.

The following non-limiting examples illustrate the invention, it being understood that examples 1 to 6 relate to the preparation of silylated compounds which can be acylated in accordance with the invention:

EXAMPLE 1

In a 1 liter, 3-neck flask fitted with stirrer, thermometer, and drying tube, 40.5 g. (0.40 mole) of triethylamine was added to a mixture of 43.2 g. (0.20 mole) of 6-APA and 425 ml. of dry acetonitrile under a nitrogen atmosphere. At 10–15°C., 25.8 g. (0.20 mole) of dimethyldichlorosilane was added dropwise, and then the mixture was stirred at 45°C. for one hour. After cooling to 15°C., the insoluble material was removed by filtration, washed with acetonitrile, and dried; weight 48.3 g. or 88% of theory for triethylamine hydrochloride. Complete water-solubility showed absence of unreacted 6-APA.

To prove that the 6-APA could be re-obtained, the clear pale yellow filtrate was poured into 500 ml. of ice-water and adjusted to pH 3.9 with 1 ml. of 2.5 N HCl. After stirring for one-half hour, the white, crystalline 6-APA was recovered by filtration and washed with water and finally with acetone; dry weight, 40.5 g. or 94% of that used as starting material; iodometric assay, 998 mcg. per mg.

EXAMPLE 2

When the procedure of Example 1 was followed, substituting other anhydrous organic solvents for acetonitrile, soluble silylated derivatives of 6-APA were obtained, as shown by regeneration of APA from the solutions as illustrated below:

	Reaction Time	Recovery of 6-APA	
Solvent Used			
Methylene chloride	3 hrs.	93%	
Chloroform (alcohol-free)	1 hr.	85%	
Ethylacetate	2 hrs.	82%	35
Dioxane	1 hr.	62%	
Methylisobutyl ketone	1 hr.	77%	

Likewise, using dimethylformamide, tetrahydrofuran, and benzene as reaction media, 6-APA was recovered.

EXAMPLE 3

A mixture of 43.2 g. of 6-APA, 425 ml. of methylene chloride and 40.5 g. of triethylamine, was treated with 25.8 g. of dimethyldichlorosilane at 10–15°C. and the mixture was refluxed gently for two hours. An indicator showed that no free triethylamine remained. After stirring at 5–10°C. for one-half hour, the insoluble by-products were removed by filtration, washed with methylene chloride and dried. Of the 44.0 g. obtained only 0.4 g. was unreacted 6-APA.

After precipitating additional triethylamine hydrochloride by adding 250 ml. of ether anhydrous and filtering, the filtrate was concentrated to dryness under reduced pressure at 25°C. The residue, 57.3 g., was freed of remaining triethylamine hydrochloride by dissolving in 290 ml. of dry ethyl acetate, filtering and re-concentrating to constant weight, 54.5 g. or 100% theory. The total amount of triethylamine hydrochloride recovered was 53.9 g. or 98% of theory. The product was a pale yellow, friable solid with a chlorine content of 0.08%.

Calculated for $C_{10}H_{16}N_2O_3SSi$: C, 44.09; H, 5.92; N, 10.29
Found: C, 42.93; H, 6.29; N, 9.60

This silylated 6-APA was completely soluble at 20°C. in anhydrous solvents such as methylene chloride, chloroform, carbon tetrachloride, ethylene dichloride, ethylacetate, tetrahydrofuran, dioxane, benzene, toluene, dimethylsulfoxide, dimethyl-

acetamide, dimethylformamide and acetonitrile, but largely insoluble in hexane and cyclohexane.

5 On treating a solution of 5.0 g. of this dimethylsilane derivative in 50 ml. of dry ethyl acetate at 5°C. with 2.5 ml. of ethyl alcohol, 6-APA crystallized; recovery 3.5 g. representing 88% of the 6-APA used as starting material; iodometric assay, 884 mcg. per mg. 5

EXAMPLE 4

10 By a procedure similar to Example 1, a mixture of 21.6 g. (0.10 mole) of 6-APA, 213 ml. of methylene chloride, and 20.3 g. (0.20 mole) of triethylamine was treated with 15.7 g. (0.10 mole) of methylpropyldichlorosilane with cooling. After refluxing gently for two hours and cooling to 15°C., the insoluble material was removed by filtration and washed with methylene chloride. Solubilization of the triethylamine hydrochloride by stirring in water left 0.4 g. of unreacted 6-APA. 10

15 Regeneration of 6-APA from the clear, pale yellow methylene chloride solution by pouring into water, filtration and washing the white product with acetone, afforded 18.8 g. of 6-APA or 87% recovery; iodometric assay, 993 mcg. per mg. 15

EXAMPLE 5

20 When the procedure of Example 4 was followed substituting equimolar amounts of other halosilanes in place of methylpropyldichlorosilane, soluble derivatives of 6-APA were obtained as shown by regeneration from the solution as illustrated below: 20

Halosilane Used	Reaction Time	Recovery of 6-APA
Methyldichlorosilane	1 hr.	84%
Phenylmethyldichlorosilane	2 hrs.	88%
25 Methyltrichlorosilane	1 hr.	52%
Diphenyldichlorosilane	3 hrs.	78%

EXAMPLE 6

30 Diphenyldichlorosilane, 25.3 g. (0.10 mole), was added dropwise at 10–15°C. to a mixture of 21.6 g. of 6-APA, 213 ml. of methylene chloride and 20.3 g. of triethylamine, and the mixture was allowed to reflux for three hours. After cooling to 10°C., the insoluble by-product was removed by filtration and washed with methylene chloride. Removal of triethylamine hydrochloride from the dried solid by solubilization in cold water left 1.6 g. of unreacted 6-APA. 30

35 The clear methylene chloride solution was concentrated to dryness under reduced pressure at 20–25°C. The residue, 46.0 g., was freed of triethylamine hydrochloride by dissolving in 200 ml. of dry ethyl acetate, filtering and reconcentrating to constant weight, 39.4 g. This product was a pale yellow, friable solid with a chlorine content of 0.33%. 35

40 Calculated for $C_{20}H_{20}N_2O_3SSi$: C, 60.58; H, 5.08; N, 7.07
Found: C, 59.77; H, 5.41; N, 6.10 40

The product was soluble at 20°C. in anhydrous solvents including CH_2Cl_2 , tetrahydrofuran, acetone, benzene and dimethylformamide.

45 On treating a solution of 10.0 g. of this silenated 6-APA derivative in 50 ml. of methylene chloride with 50 ml. of cold water, 6-APA crystallized; recovery 3.75 g. corresponding to 72% from the 6-APA used as a starting material; iodometric assay, 976 mcg. per mg. 45

EXAMPLE 7

Ampicillin

50 A methylene chloride solution of silenated 6-APA was prepared from 0.20 mole of 6-APA as described in Example 3. Without removing triethylamine hydrochloride by filtration, the mixture was treated with 26.7 g. of N,N-dimethylaniline, and then 41.9 g. (0.203 mole) of D(–)-phenylglycyl chloride hydrochloride was added portionwise over 20 minutes at 0°C. and then allowed to warm to 20°C. and to stir at that temperature for 15 minutes. After pouring the reaction mixture into 1200 ml. of cold water with stirring, the resulting two-phase solution (pH 1.8) was clarified by filtration and 150 ml. of ethylacetate was added to the filtrate. 55

To this mixture at 5–10°C., a solution of β -naphthalenesulfonic acid containing 52 g. (0.25 mole) of active agent was added dropwise while adding dilute sodium

	8	9	1,266,544	24	9
hexane and 50 ml. of d; recovery etric assay,	5	5	hydroxide solution concurrently to maintain a pH of 1.5—1.7. After stirring over- night, the white crystalline product was collected by filtration and washed thoroughly with cold water and finally with ethyl acetate. A sample of the wet filter cake dried in a vacuum oven at 50—60°C. showed the wet filter cake to contain 106 g. of the β -naphthalene sulfonic acid salt of ampicillin or 95% of theory based on APA.	5	
(mole) of 6- amine was After re- is removed ethylamine	10	10	The wet filter cake was heated in a mixture of 220 ml. of isopropanol and 19.4 g. of triethylamine at 70—78°C. for 15 minutes, filtered, and the product washed with 85% isopropanol. The yield of dried ampicillin anhydrous amounted to 58.0 g. or 83% of theory from 6-APA; iodometric assay, 1010 mcg. per mg.; bioassay, 1015 mcg. per mg.	10	
le solution afforded	15	15	Comparable results were obtained when the N,N-dimethylaniline was added prior to the addition of dimethyldichlorosilane and the reaction time at reflux was reduced to one hour. In other analogous experiments, ampicillin was prepared when the quantity of dimethyldichlorosilane was decreased to 14.2 g. (0.11 mole) and increased to 51.7 g. (0.40 mole) and when the triethylamine was replaced by 2,2'-diethyldihexylamine.	15	
r amounts ves of 6- d below:	20	20	EXAMPLE 8 Ampicillin To 580 ml. of methylene chloride containing 0.043 mole of anhydrous am- monia, 43.2 g. of 6-APA and 26.7 g. of N,N-dimethylaniline were added followed by the dropwise addition of 25.8 g. of dimethyldichlorosilane at 12°C. After re- fluxing gently for one hour, the mixture was cooled to 10°C., under nitrogen, and 13 ml. of 3.1 N solution of dimethylaniline dihydrochloride in methylene chloride was added to inactivate excess ammonia.	20	
	25	25	At 0°C., 41.9 g. of D(-)-phenylglycyl chloride hydrochloride was added portion- wise over 20 minutes. After stirring at 0°C. for an additional 15 minutes, the reaction mixture was poured into 1200 ml. of ice-water and converted to ampicillin an- hydrous as described in Example 7; yield, 80% of theory; bioassay, 987 mcg. per mg.	25	
—15°C. 0.3 g. of ooling to methylene lubiliza-	30	30	EXAMPLE 9 6-(1-Aminocyclohexanecarboxamido)Penicillanic Acid A methylene chloride solution of silenated 6-APA was prepared from 0.20 mole of APA as described in Example 3. Without removing triethylamine hydrochloride by filtration, the mixture was treated with 16.6 g. of pyridine, and then 40.7 g. (0.205 mole) of 1-amino-1-cyclohexanecarboxylic acid chloride hydrochloride was added portionwise over 20 minutes at 0°C. After stirring at 0°C. and finally at 20°C for one hour, the reaction mixture was poured into 400 ml. of water, clarified by filtration, and adjusted to pH 5.4 by adding dilute sodium hydroxide solution.	30	
reduced chloride constant content	35	35	After stirring overnight at 20°C., the product was collected by filtration, washed and dried; yield as dihydrate was 59.0 g. or 78% of theory; purity 95% by iodo- metric assay.	35	
	40	40	EXAMPLE 10 6-(2-Amino-2-Indancarboxamido)Penicillanic Acid A methylene chloride solution of silenated 6-APA was prepared from 0.10 mole of APA as described in Example 3. After removing triethylamine hydrochloride by filtration, 13.4 g. of N,N-dimethylaniline was added to the filtrate followed by the addition of 24.2 g. (0.104 mole) of 2-amino-2-carboxyindane acid chloride hydro- chloride in small portions over 20 minutes at 0°C. The mixture was allowed to warm to room temperature and stir for an additional 15 minutes.	40	
tetra-	45	45	After pouring the amber solution into 200 ml. of ice-water and filtering the mixture, the filtrate was adjusted to pH 5.8 with dilute sodium hydroxide solution. After stirring for 16 hours, the white product was collected by filtration, washed with water and acetone, and then dried; yield, 18.6 g. or 50% of theory. The purity was 96% as determined by iodometric assay.	45	
0 ml. of 3.75 g. c assay,	50	50	EXAMPLE 11 Ampicillin Substituting 23.0 g. (0.20 mole) of methylchlorosilane ($\text{CH}_3\text{SiHCl}_2$) for di- methyldichlorosilane in the procedure of Example 7, 48.0 g. of ampicillin anhydrous, corresponding to 69% of theory, was obtained, iodometric assay, 1004 mcg. per mg.	50	
0 mole chloride d then ortion- at that of cold filtra-	55	55		55	
aining odium					

EXAMPLE 12

Following the procedure of Example 9, but substituting for 1-aminocyclohexane carboxylic acid chloride hydrochloride as acylating agent, equivalent amounts of other acylating agents, a series of penicillin derivatives, and therefrom the corresponding penicillins, are obtained as set forth in Table B below:

Table B

Acylating Agents Used	Final Penicillins obtained
1-aminocyclopentanecarboxylic acid chloride HCl	6-(1-aminocyclopentanecarboxamido)penicillanic acid
2-amino-1,2,3,4-tetrahydro-6-methoxy-2-naphthoic acid chloride HCl	6-(2-amino-1,2,3,4-tetrahydro-6-methoxy-2-naphthamido)penicillanic acid
2-amino-1,2,3,4-tetrahydro-7-ethoxy-2-naphthoic acid chloride HCl	6-(2-amino-1,2,3,4-tetrahydro-7-ethoxy-2-naphthamido)penicillanic acid
2-amino-4-phenyl-2-indan-carboxylic acid chloride HCl	6-(indan-4-phenyl-2-carboxamido)penicillanic acid
2-amino-3-phenoxy-2-indan-carboxylic acid chloride HCl	6-(indan-2-amino-3-phenoxy-2-carboxamido)penicillanic acid
2-amino-4-butyl-2-indan-carboxylic acid chloride HCl	6-(indan-2-amino-4-butyl-2-carboxamido)penicillanic acid
1-amino-7-methyl-1-indan-carboxylic acid chloride HCl	6-(indan-1-amino-7-methyl-1-carboxamido)penicillanic acid

EXAMPLE 13

Penicillin V

Methyldichlorosilane, 23.0 g. (0.20 mole), was added dropwise at 10—15°C. to a mixture of 43.2 g. of 6-APA, 425 ml. of methylene chloride, and 40.5 g. of triethylamine, and the mixture was heated at reflux for one hour. After cooling to 10°C. and removing triethylamine hydrochloride by filtration, the solution was treated with 26.7 g. of N,N-dimethylaniline, and then a solution of 34.0 g. (0.20 mole) of phenoxyacetyl chloride in 100 ml. of methylene chloride was added at 0°C. over 20 minutes. The mixture was allowed to stir at 20°C. for 1½ hours.

After pouring the clear red solution into 800 ml. of ice-water containing 80 g. of sodium bicarbonate, the layers were separated, and the methylene chloride layer re-extracted with water. Acidification of the aqueous phase with acetic acid and finally to pH 1.8 with dilute hydrochloric acid afforded nearly colourless crystals; yield 49.0 g. or 70% of theory; purity by iodometric assay, 95%.

EXAMPLE 14

6-(1-Aminocyclohexanecarboxamido)penicillanic acid

A methylene chloride solution of the methyl hydrogen silane derivative of 6-APA was prepared as described in Example 13. Without filtration, the mixture was treated with 17.4 g. of pyridine and acylated with 40.7 g. of 1-amino-1-cyclohexanecarboxylic acid chloride hydrochloride as described in Example 9. Crystallisation of the product from a mixture of 200 ml. of water and 200 ml. of isopropyl alcohol afforded 39.2 g. as the dihydrate; bioassay, 888 mcg. per mg.

EXAMPLE 15

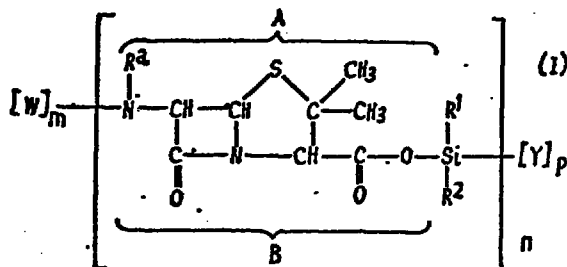
Dioloxacillin Acid

A methylene chloride solution of the methyl hydrogen silane derivative of 6-APA was prepared as described in Example 13. After filtration, the solution was treated with 26.7 g. of N,N-dimethylaniline, and then a solution of 58.2 g. (0.20 mole) of 3-(2,6-dichlorophenyl)-5-methylisoxazole-4-carbonyl chloride in 80 ml. of methylene chloride was added at 0°C. over 15 minutes. The mixture was allowed to warm to room temperature and stir for an additional hour.

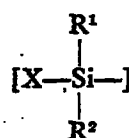
After pouring the reaction mixture into 500 ml. of ice-water and separating the layers, the dried methylene chloride layer was treated with 700 ml. of hexane to crystallise the product. The resulting Dicloxacillin acid, after drying, amounted to 67 g. or 71% of theory.

WHAT WE CLAIM IS:—

1. A process for the preparation of novel acylated organo-silane penicillins of the general formula:

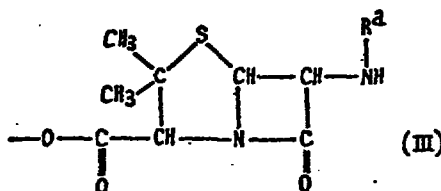


wherein R¹ is hydrogen, alkyl, aryl or aralkyl, R² is halogen, alkyl, aryl or aralkyl; R^a is an acyl residue of an organic carboxylic acid; W is hydrogen or a radical of the formula:



(II)

(wherein R¹ and R² have the meanings defined above and X is halogen) m is 0 or 1; n is an integer from 1 to 25; p is 0 or 1; and Y is halogen or a group of the formula:



(wherein R^a has the meaning defined above) with the provisos that, in formula (I):

- (1) when m is 0 and p is 0, n is more than 1 and the two free valencies are joined together to complete a cyclic compound
- (2) when n is more than 1, the moieties A of the additional groups B recur in random head-toward-head, head-toward-tail and tail-toward-tail disposition;
- (3) W is not hydrogen when n is 1, and Y is of formula (III);
- (4) m and p are always equal; and
- (5) when R¹ and R² are both selected from alkyl, aryl and aralkyl, R^a contains an amino group on the α-carbon atom to the carbonyl group of the acyl residue.

which comprises acylating a corresponding organosilane 6-amino-penicillanic acid derivative of general formula (I), in which R¹, R², W, m, n, p and Y have the meanings defined above and provisos (1), (2), (3) and (4) apply but in which R^a is a hydroxy group, with a reactive derivative of an organic carboxylic acid R^b-CO-OH (where R^b-CO- is an acyl group it being understood that R^b contains an amino group on the α-carbon atom to the carboxyl group when the organosilane 6-amino-penicillanic acid derivative being acylated has both of R¹ and R² selected from alkyl, aryl and aralkyl groups).

2. A process as claimed in Claim 1, wherein R¹ is hydrogen, lower alkyl, phenyl,

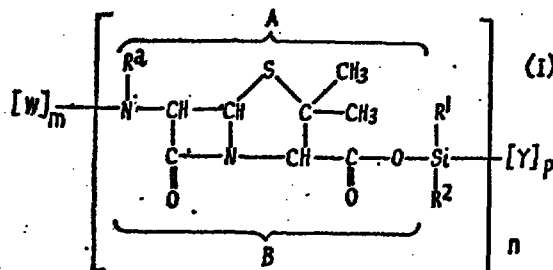


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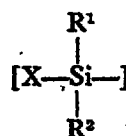
After pouring the reaction mixture into 500 ml. of ice-water and separating the layers, the dried methylene chloride layer was treated with 700 ml. of hexane to crystallise the product. The resulting Dicloxacillin acid, after drying, amounted to 67 g. or 71% of theory.

WHAT WE CLAIM IS:—

1. A process for the preparation of novel acylated organo-silane penicillins of the general formula:

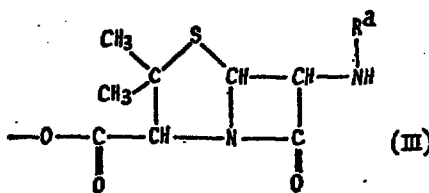


wherein R¹ is hydrogen, alkyl, aryl or aralkyl, R² is halogen, alkyl, aryl or aralkyl; R^a is an acyl residue of an organic carboxylic acid; W is hydrogen or a radical of the formula:



(II)

(wherein R¹ and R² have the meanings defined above and X is halogen) m is 0 or 1; n is an integer from 1 to 25; p is 0 or 1; and Y is halogen or a group of the formula:



(wherein R^a has the meaning defined above) with the provisos that, in formula (I):

- (1) when m is 0 and p is 0, n is more than 1 and the two free valencies are joined together to complete a cyclic compound
- (2) when n is more than 1, the moieties A of the additional groups B recur in random head-toward-head, head-toward-tail and tail-toward-tail disposition;
- (3) W is not hydrogen when n is 1, and Y is of formula (III);
- (4) m and p are always equal; and
- (5) when R¹ and R² are both selected from alkyl, aryl and aralkyl, R^a contains an amino group on the α-carbon atom to the carbonyl group of the acyl residue.

which comprises acylating a corresponding organosilane 6-amino-penicillanic acid derivative of general formula (I), in which R¹, R², W, m, n, p and Y have the meanings defined above and provisos (1), (2), (3) and (4) apply but in which R^a is a hydroxy group, with a reactive derivative of an organic carboxylic acid R^b—CO—OH (where R^b—CO— is an acyl group; it being understood that R^b contains an amino group on the α-carbon atom to the carboxyl group when the organosilane 6-amino-penicillanic acid derivative being acylated has both of R¹ and R² selected from alkyl, aryl and aralkyl groups).

2. A process as claimed in Claim 1, wherein R¹ is hydrogen, lower alkyl, phenyl,



* C L M S *

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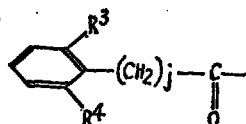
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lower alkylphenyl or benzyl, R^3 is halogen, lower alkyl, phenyl lower alkylphenyl or benzyl and the term "lower" alkyl means that the radical contains 1 to 6 carbon atoms.

5 3. A process as claimed in Claim 1 or Claim 2, wherein R^1 and R^2 are not both selected from alkyl, aryl and aralkyl. 5

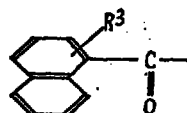
4. A process as claimed in Claim 3, wherein the reactive derivative of an organic carboxylic acid is the N-carboxy anhydride.

5. A process as claimed in any of Claims 1 to 4 wherein $R^b\text{—CO—}$ is



10 wherein R^3 and R^4 each is hydrogen or lower alkoxy and j is 0 or 1. 10

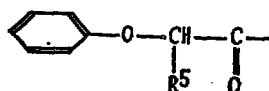
6. A process as claimed in any of Claims 1 to 3, wherein $R^b\text{—CO—}$ is



wherein R^3 has the meaning defined in Claim 5.

7. A process as claimed in any of Claims 1 to 4 wherein $R^b\text{—CO—}$ is

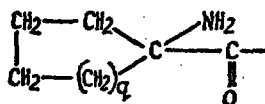
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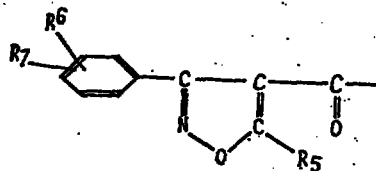
wherein R^5 is hydrogen, lower alkyl containing 1 to 6 carbon atoms or phenyl.

8. A process as claimed in any of Claims 1 to 4, wherein $R^b\text{—CO—}$ is



wherein q is an integer of from 1 to 5.

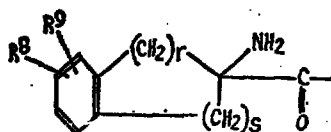
20 9. A process as claimed in any of Claims 1 to 3, wherein $R^b\text{—CO—}$ is 20



wherein R^5 has the meaning defined in Claim 7 and R^6 and R^7 are hydrogen or halogen.

10. A process as claimed in any of Claims 1 to 4, wherein $R^b\text{—CO—}$ is

25



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wherein R^8 and R^9 are hydrogen, lower alkyl containing 1 to 6 carbon atoms, lower alkoxy containing 1 to 6 carbon atoms, phenyl or phenoxy, r is 0 or 1, and s is an

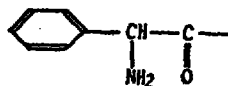


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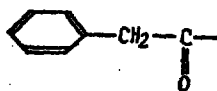
integer from 1 to 3, with the provisos that, when r is 0, s is greater than 1, and when r is 1, s is less than 3.

11. A process as claimed in any of Claims 1 to 4 wherein R^b -CO- is



12. A process as claimed in Claim 9 wherein R^5 is a methyl radical and R^6 and R^7 are chlorine atoms in the 2- and 6-positions.

13. A process as claimed in any one of Claims 1 to 3 in which R^3 is of the formula



14. A process as claimed in Claim 5 in which R^3 and R^4 are methoxy and $j=0$.

15. A process as claimed in Claim 7 in which R^5 is ethyl.

16. A process as claimed in Claim 8 in which $q=1$.

17. A process as claimed in Claim 6, wherein R^3 is an ethoxy radical.

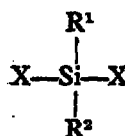
18. A process as claimed in Claim 8, wherein q is 2.

19. A process as claimed in Claim 7, wherein R^5 is hydrogen.

20. A process as claimed in Claim 10, wherein R^8 and R^9 are hydrogen, and r and s are both equal to 1.

21. A process as claimed in any of the preceding claims, wherein the acylation is carried out in an anhydrous non-hydroxylic organic solvent in the presence of an acid acceptor.

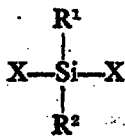
22. A process as claimed in any of the preceding claims, wherein the organosilane starting material of general formula (I) in which R^a is a hydrogen atom is obtained by reacting 6-aminopenicillanic acid or a salt thereof, with a di- or tri-halosilane of the following formula:



(wherein R^1 and R^2 have the meanings defined in Claim 1 and X is a halogen atom) preferably in an anhydrous non-hydroxylic organic solvent and preferably in the presence of an acid acceptor.

23. A process as claimed in Claim 22, wherein the molar proportions of the 6-aminopenicillanic acid or salt thereof to the di- or tri-halosilane to the said acid acceptor are substantially 1:1:2.

24. A process for preparing organosilane penicillins in which 6-amino-penicillanic acid or a salt thereof is reacted with a di- or tri-halosilane of formula

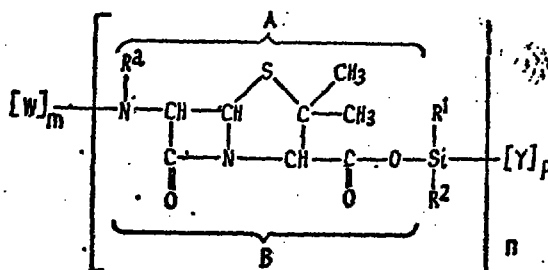


wherein R^1 is hydrogen, alkyl, aryl or aralkyl; R^2 is halogen, alkyl, aryl or aralkyl and X is halogen and the organosilane derivative of 6-aminopenicillanic acid produced is acylated by a reactive derivative of an organic carboxylic acid R^b .COOH (where R^b CO is an acyl group), R^b containing an amino group when R^1 and R^2 are both selected from alkyl, aryl and aralkyl groups.

25. A process for the preparation of organosilane penicillins substantially as described herein and shown with reference to any one of Examples 7 to 12.

26. An organosilane penicillin when prepared by the process claimed in any one of Claims 1 to 25.

27. An organosilane penicillin of the general formula



(II)

wherein R^1 , R^2 , W , m , n , p , and Y have the meanings defined in Claim 1, R^a is an acyl residue of an organic carboxylic acid and the provisos (1) to (5) specified in claim 1 apply.

28. Compounds as claimed in Claim 27, wherein R^1 is hydrogen, methyl or phenyl, R^2 is methyl, propyl, phenyl or chlorine.

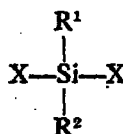
29. Compounds as claimed in claim 27, wherein R^1 is methyl R^2 is chlorine.

30. Compounds as claimed in Claim 27 or Claim 28, wherein R^a has the meaning defined for R^b -CO- in any of Claims 5 to 20.

31. A process for the preparation of a penicillin acid or salt thereof, which comprises subjecting a compound as claimed in any of Claims 26 to 30 to hydrolysis or alcoholysis and if desired converting the acid obtained to a salt.

32. A process for the preparation of a penicillin substantially as described herein and shown with reference to any of Examples 7 to 12.

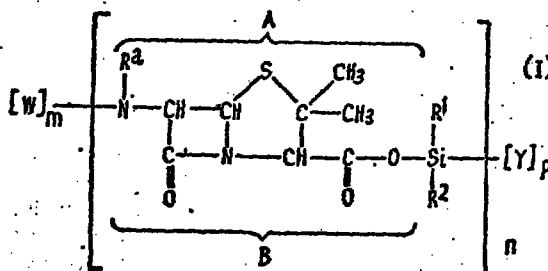
33. A process for the preparation of a penicillin or salt thereof which comprises reacting 6-aminopenicillanic acid or a salt thereof with a di- or tri-halosilane of formula:



wherein R^1 is hydrogen, alkyl, aryl or aralkyl; R^2 is halogen, alkyl, aryl or aralkyl and X is halogen and the organosilane derivative of 6-aminopenicillanic acid produced is acylated by a reactive derivative of an organic carboxylic acid R^b .COOH (where R^b CO is an acyl group), R^b containing an amino group when R^1 and R^2 are both selected from alkyl, aryl and aralkyl groups and the organosilane penicillin product is subjected to hydrolysis or alcoholysis and if desired converting the acid obtained to a salt.

34. A penicillin or salt thereof when prepared by the process claimed in any one of Claims 31 to 33.

35. An organosilane 6-aminopenicillanic acid derivative of the general formula:



(I)



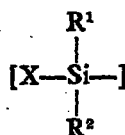
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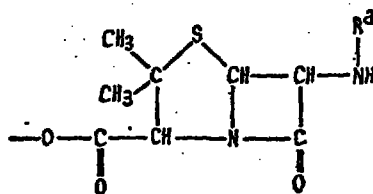
wherein R¹ is hydrogen, alkyl, aryl or aralkyl; R² is halogen, alkyl, aryl or aralkyl; R^a is hydrogen; W is hydrogen or



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wherein R¹ and R² have the meanings defined above and X is halogen; m is 0 or 1; n is an integer from 1 to 25; p is 0 or 1; Y is halogen or a group of the formula:

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(II)

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(wherein R^a has the meaning defined above) with the provisos that, in formula (I).

(a) when m is 0 and p is 0, n is more than 1 and the two free valencies are joined together to complete a cyclic compound;

(b) when n is more than 1, the moieties A of the additional groups B recur in random head-toward-head, head-toward-tail and tail-toward-tail disposition;

10

(c) m is always equal to p.

(d) when R¹ is alkyl, aryl or aralkyl, R² is halogen.

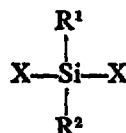
36. Compounds as claimed in Claim 35, wherein R¹ is methyl and R² is chlorine.

37. Compounds as claimed in Claim 35, wherein R¹ is hydrogen and R² is methyl.

15

38. A process for the preparation of an organosilane 6-aminopenicillanic acid derivative which comprises reacting 6-aminopenicillanic acid or a salt thereof with a di- or tri-halosilane of the following formula:

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(wherein R¹ and R² have the meanings defined in Claim 35 and X is a halogen atom with the proviso that when R¹ is alkyl, aryl or aralkyl, R² is halogen) preferably in an anhydrous nonhydroxylic organic solvent and preferably in the presence of an acid acceptor.

39. A process as claimed in Claim 38 wherein the molar proportions of the 6-aminopenicillanic acid or salt thereof to the di- or tri-halosilane to the said acid acceptor are substantially 1:1:2.

25

40. A process for preparing organosilane 6-aminopenicillanic acid derivatives substantially as described herein and shown with reference to any one of Examples 1 to 9, 11 and 12.

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41. An organosilane 6-aminopenicillanic acid derivative when prepared by the process claimed in any one of Claims 38 to 40.

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42. A process for the preparation of organosilane penicillins substantially as described herein and shown with reference to any one of Examples 13 to 15.

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43. An organosilane penicillin prepared by a process according to Claim 42.

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44. A process for the preparation of a penicillin substantially as described herein and shown with reference to any one of Examples 13 to 15.

45. A penicillin prepared by a process according to Claim 44.

46. A process for preparing organosilane 6-aminopenicillanic acid derivatives substantially as described herein and shown with reference to any one of Examples 13 to 15.

5 47. An organosilane 6-aminopenicillanic acid derivative prepared by a process according to Claim 46. 5

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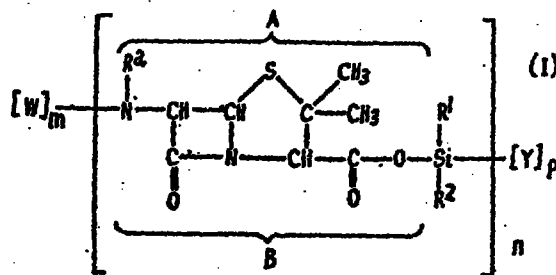
SPECIFICATION NO 1266544

The following corrections were allowed under Section 76 on 17 December 1973.

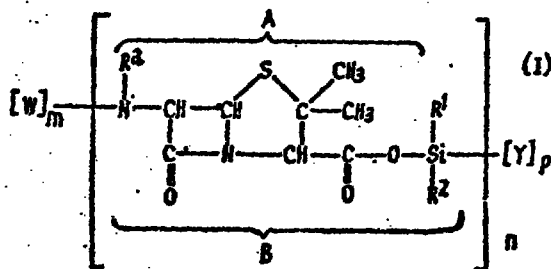
Page 2, line 1

Page 11, line 8

Page 14, lines 6 and 34, delete



insert



Attention is also directed to the following printers errors:-

Page 4, lines 24 and 25, for solenation read silenation

Page 6, line 19, for 2- aminocyclohexanecarboxylic read 1-aminocyclohexanecarboxylic

Page 7, line 3, for phenylglycol read phenylglycyl

Page 10, line 47, for Dioloxacillin read Diclloxacillin

THE PATENT OFFICE
17 January 1974

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