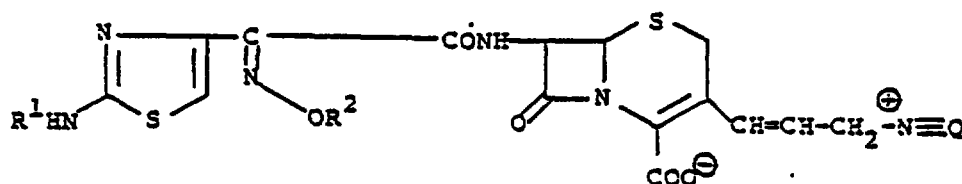
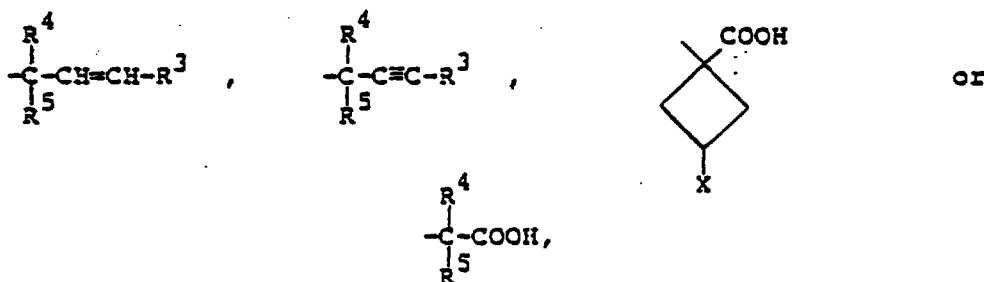


CEPHALOSPORIN DERIVATIVE INTERMEDIATES

This application has been divided out of our Application No.84.03474, referred to below as our "primary" Application, which relates to novel cephalosporin derivatives of the formula



wherein R^1 is hydrogen or a conventional amino-protecting group, R^2 is hydrogen, a straight or branched chain alkyl group containing from 1 to 4 carbon atoms or a group of the formula



in which R^3 is hydrogen, (lower)alkyl or carboxyl, X is halogen, hydroxy or (lower)alkoxy, and R^4 and R^5 are each independently hydrogen, methyl or ethyl, or R^4 and R^5 , taken together with the carbon atom to which they are attached, may be a cycloalkylidene ring containing from 3 to 5 carbon atoms, and

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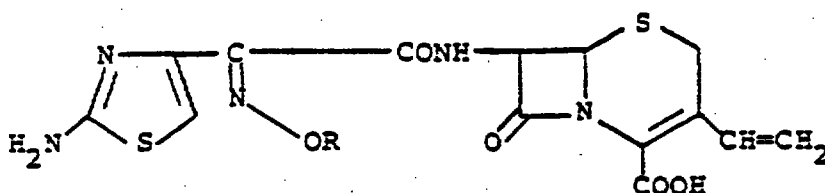


is a quaternary ammonio group, and to nontoxic pharmaceutically acceptable salts, physiologically hydrolyzable esters and solvates thereof.

The present invention provides intermediates for the preparation of the compounds of Formula I and a process for the preparation of these intermediates.

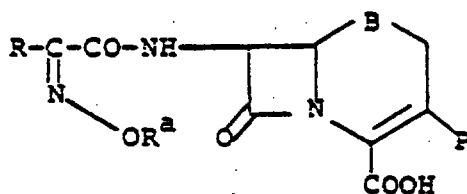
Background and Prior Art

A) Published European Patent Application No. 30,630 discloses a vast number of 7-acylamino-3-vinylcephalosporanic acid derivatives including, inter alia, those of the formula

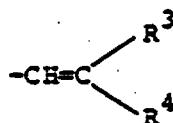


wherein R inter alia may be (lower)alkyl, (lower)alkenyl, (lower)alkynyl or carboxy(lower)alkyl. The compounds are prepared, inter alia, by reaction of the corresponding 3-halomethyl compound with a triarylphosphine, followed by treatment with a base and reaction with formaldehyde. In each case, the final 3-substituent is the vinyl group. There is no disclosure or suggestion of a quaternary ammonio-substituted propenyl moiety for the 3-substituent.

B) U.K. Patent Specification No. 1,399,086 contains a generic disclosure encompassing a vast number of cephalosporins of the formula

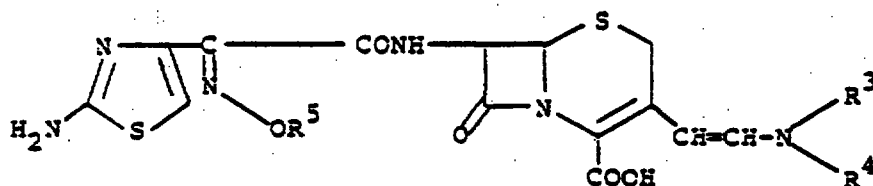


wherein R is hydrogen or an organic group, R^a is an etherifying monovalent organic group linked to the oxygen through a carbon atom, B is >S or >S-O, and P is an organic group. In one embodiment, P may be inter alia a vinyl group of the formula



in which R³ and R⁴ independently may be hydrogen, nitrile, (lower)-alkoxycarbonyl, or substituted or unsubstituted aliphatic, cycloaliphatic, araliphatic or aromatic. However, the 2-aminothiazol-4-yl group is not identified as a possible R substituent and there is no disclosure or suggestion that P may be a quaternary ammonio-substituted propenyl group. U.S. Patent 3,971,778 and its divisionals Nos. 4,024,133, 4,024,137, 4,064,346, 4,033,950, 4,079,178, 4,091,209, 4,092,477 and 4,093,803 have similar disclosures.

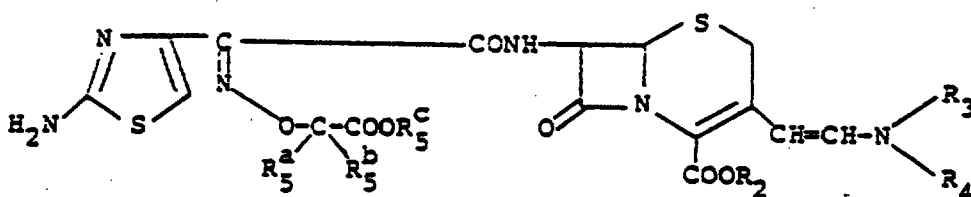
C) U.S. Patent No. 4,307,233 discloses, inter alia, 3-vinyl cephalosporin derivatives of the formula



in which R⁵ inter alia may be alkyl, vinyl, cyanomethyl or a protective group such as 2-methoxyprop-2-yl, and R³ and R⁴ are alkyl groups (optionally substituted by hydroxy, alkoxy, amino, alkylamino or dialkylamino) or phenyl groups, or R³ and R⁴, taken together with the nitrogen to which they are attached, may form a saturated heterocyclic ring of 5 or 6 members, optionally containing another hetero-atom selected from N, O and S, and optionally substituted by an alkyl group. The compounds are useful as intermediates in the preparation of 3-thiovinyl cephalosporin derivatives. There is no disclosure or suggestion of a quaternary ammonio-substituted propenyl moiety for the 3-

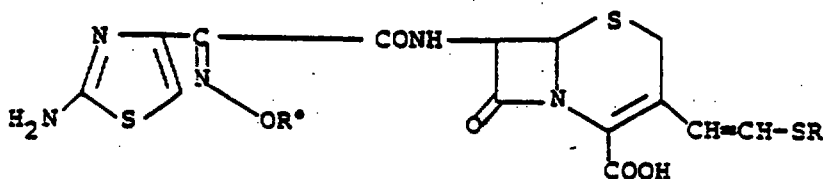
substituent. Published United Kingdom Patent Application No. 2,051,062 is concordant thereto and has a similar disclosure.

D) Published European Patent Application No. 53,537 discloses, inter alia, 3-vinylcephalosporin derivatives of the formula



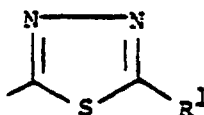
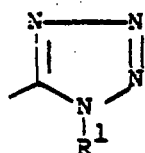
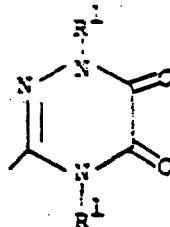
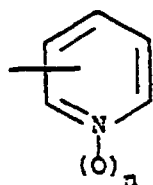
in which R_5^a and R_5^b are the same or different and are hydrogen or alkyl, or taken together, form an alkylene group containing 2 or 3 carbon atoms, R_5^c is an acid protecting group, R_2 is an acid protecting group such as an ester, R_3 and R_4 are the same or different and are hydrogen, alkyl (optionally substituted by hydroxy, alkoxy, amino, alkylamino or dialkylamino) or phenyl groups, or R_3 and R_4 , taken together with the nitrogen to which they are attached, may form a saturated heterocyclic ring of 5 or 6 members, optionally containing another hetero-atom selected from N, O and S, and optionally substituted by an alkyl group. The compounds are useful as intermediates in the preparation of 3-thiovinyl cephalosporin derivatives. There is no disclosure or suggestion of a quaternary ammonio-substituted propenyl group for the 3-substituent.

E) U.S. Patent No. 4,307,116 discloses 3-thiovinyl-cephalosporins of the formula



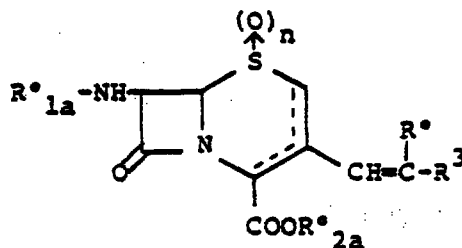
in which R^* is hydrogen, alkyl, vinyl or cyanomethyl, and R

inter alia may be one of a vast number of heterocyclic rings such as

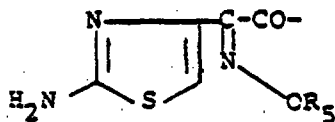


or the like. However, in each case, the heterocyclic ring is attached to the sulfur atom via a carbon atom of the heterocyclic ring. There is no disclosure or suggestion of a quaternary ammonio-substituted propenyl moiety for the 3-substituent. Although not formally related, published European Patent Application No. 53,961 has a similar disclosure, but includes 2-carboxyprop-2-yl, 1-carboxycyclobut-1-yl and the like as possible meanings of R^* .

F) Published European Patent Application No. 53,074 generically discloses a vast number of 3-vinylcephalosporin derivatives of the formula



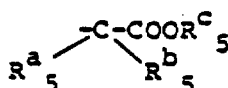
wherein R^*_{1a} (in one of several embodiments) may be



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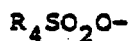
-6-

in which R_5 inter alia may be hydrogen, alkyl, vinyl, cyanomethyl, an oxime-protecting group such as trityl, etc., or a group of the formula



in which R_5^a and R_5^b are the same or different, and may be hydrogen, alkyl or, taken together, an alkylene radical of 2 or 3 carbon atoms, and R_5^c is hydrogen or an acid-protecting radical; R_{2a}^* is hydrogen or an acid-protecting radical such as methoxymethyl;

R^* (in one of several embodiments) may be a methyl group substituted by a 5- or 6-membered aromatic heterocyclic ring containing a single hetero atom, such as 2- or 3-pyridyl, 2- or 3-thienyl or 2- or 3-furyl; and R_3 is a group of the formula



in which R_4 may be alkyl, trihalomethyl or optionally substituted phenyl.

These compounds are stated to be intermediates in the preparation of compounds in which the 3-substituent is a group of the formula

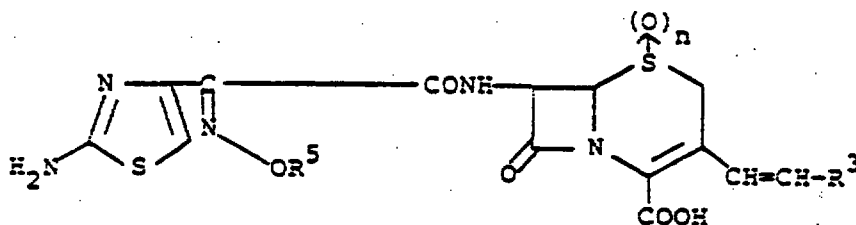


which are stated to have antibacterial activity.

Although this patent includes the possibility of R^* being a methyl group substituted by an N-containing heterocyclic ring, in both the intermediates and final products (thus giving a heterocyclic-substituted propenyl moiety), it teaches only that the heterocyclic ring is attached via one of its carbon atoms. Thus, there is no suggestion of a quaternary ammonio-

substituted propenyl group. The reference exemplifies R⁶ in the intermediates and final products only as methyl. Further, in both the intermediates and final product, the propenyl group must contain a second substituent (-O₃SR⁴ or -SR, respectively).

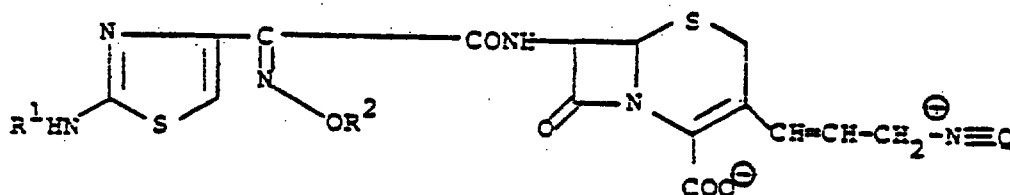
G) Published European Patent Application No. 53,538 discloses, inter alia, 3-vinylcephalosporin intermediates of the formula



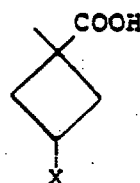
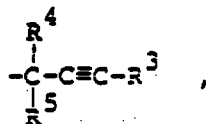
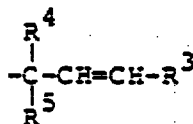
in which n is 0 or 1, R⁵ is hydrogen, alkyl, vinyl, cyanomethyl or an oxime-protecting group, and R³ is halogen.

Complete Disclosure

As indicated above, the present invention provides intermediates for the preparation of compounds of the formula

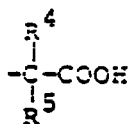


wherein R¹ is hydrogen or a conventional amino-protecting group, R² is hydrogen, a straight or branched chain alkyl group containing from 1 to 4 carbon atoms or a group of the formula



or

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in which R^3 is hydrogen, (lower)alkyl or carboxyl, X is halogen, hydroxy or (lower)alkoxy, and R^4 and R^5 are each independently hydrogen, methyl or ethyl, or R^4 and R^5 , taken together with the carbon atom to which they are attached, may be a cycloalkylidene ring containing from 3 to 5 carbon atoms, and



is a quaternary ammonio group, and nontoxic pharmaceutically acceptable salts and physiologically hydrolyzable esters thereof.

From the present intermediates one may also obtain solvates (including hydrates) of the compounds of Formula I, as well as the tautomeric forms of the compounds of Formula I, e.g. the 2-iminothiazolin-4-yl form of the 2-aminothiazol-4-yl moiety.

In another aspect, this application relates to a process for the preparation of the present intermediates.

As shown in the structural formula, the compounds of Formula I have the "syn" or "Z" configuration with respect to the alkoxyimino group. Because the compounds are geometric isomers, some of the "anti" isomer may also be present. Typically

the compounds of Formula I contain at least 90% of the "syn" isomer. Preferably the compounds of Formula I are "syn" isomers which are essentially free of the corresponding "anti" isomers.

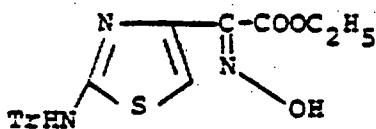
In addition to geometric isomers possible with respect to the alkoxyimino group, the compounds of Formula I (and the intermediates of Formulae IX and X) also form geometric (cis and trans) isomers about the double bond of the propenyl group. Both

the cis ("Z") and trans ("E") isomers of these compounds are contemplated herein.

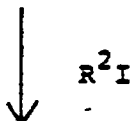
The reader requiring further details of the compounds of the formula I obtainable from the present intermediates, including details of the antibacterial properties of compounds of formula I, is referred to the specification of our primary application No.84.03474 (2134522).

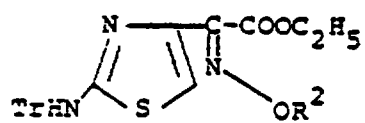
Intermediates falling within the ambit of the present invention, having protecting groups at certain points in their molecule, appear as compounds IX and X in the following Reaction Scheme 1, which represents a preferred procedure for the preparation of compounds of Formula I. In the reaction scheme, m may be 0 or 1. The abbreviation "Tr" represents the trityl (triphenylmethyl) group, which is a preferred amino-protecting group. The abbreviation "Ph" represents the phenyl group. Thus, the $-\text{CH}(\text{Ph})_2$ moiety is the benzhydryl group, which is a preferred carboxyl-protecting group. When R^2 contains a carboxyl group, it is desirable to protect the carboxyl group with a conventional carboxyl-protecting group such as the t-butyl moiety.

Reaction Scheme 1

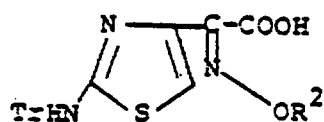
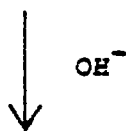


II

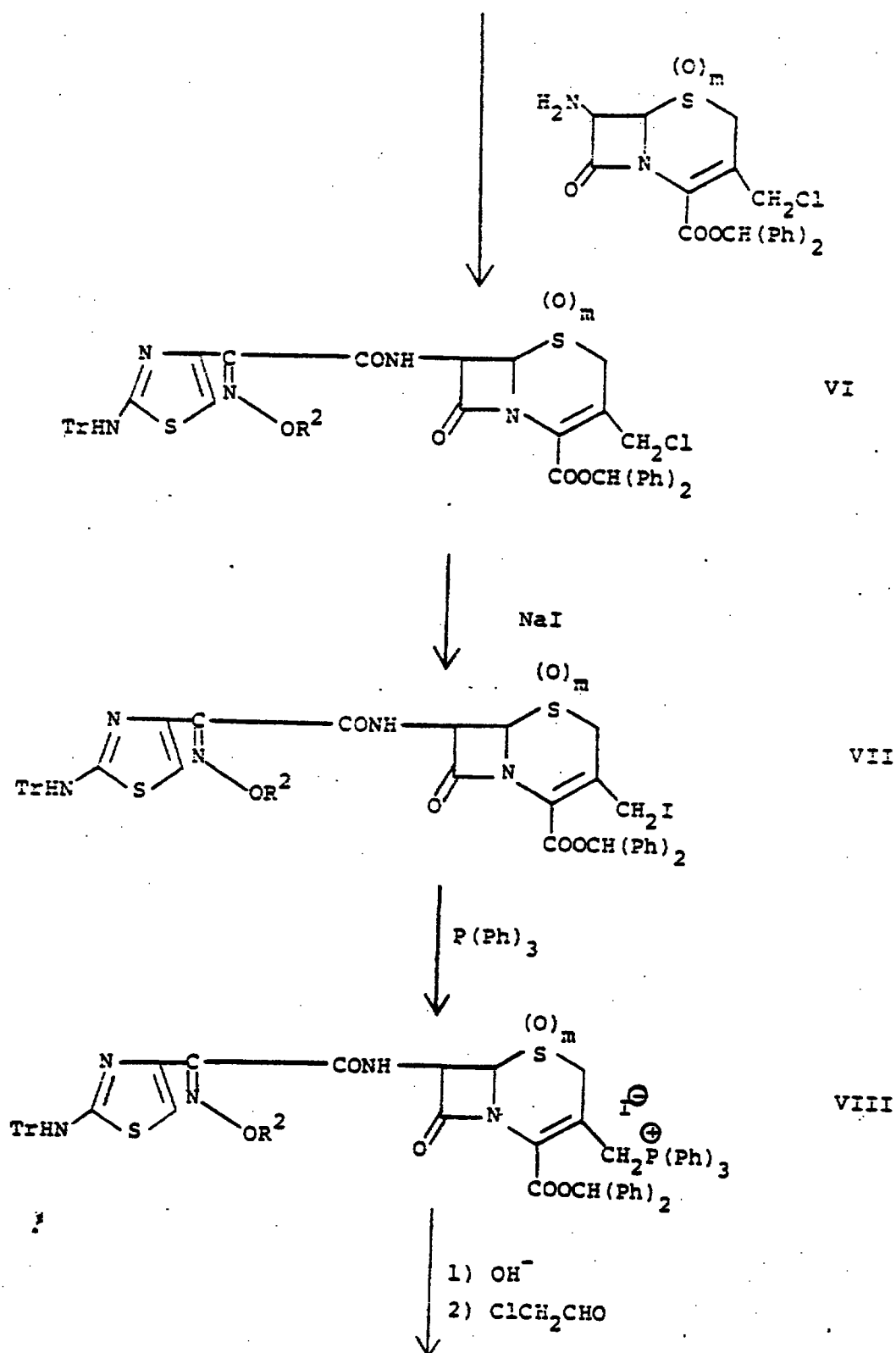


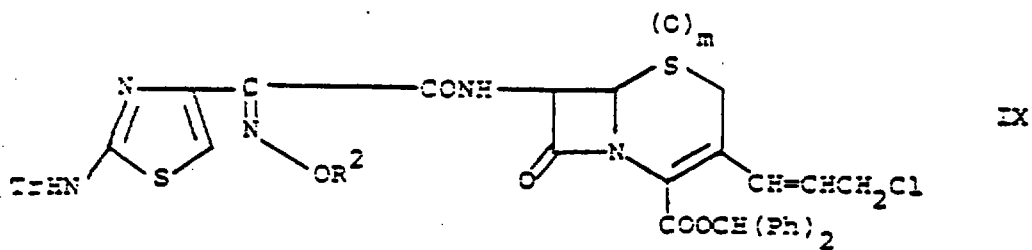


III

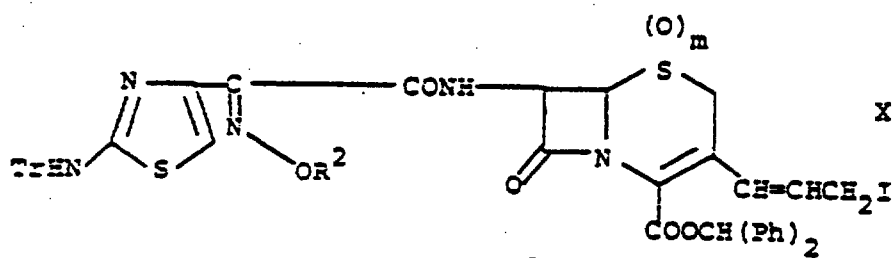


IV

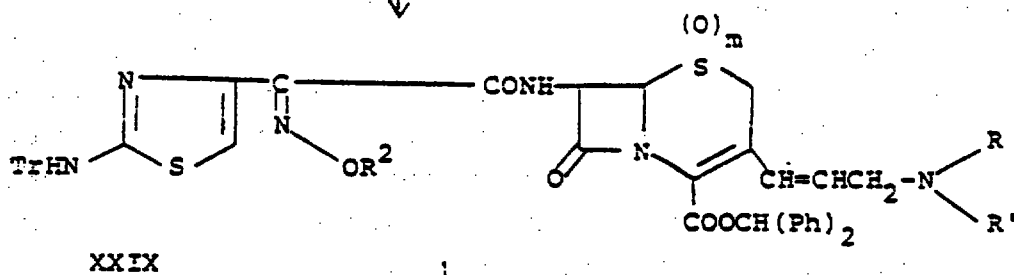




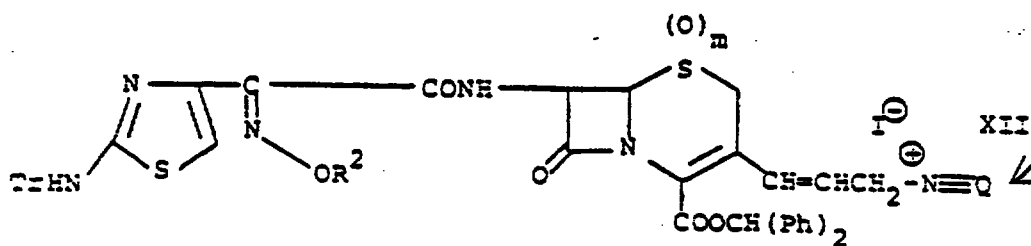
NaI



$\text{HN} \begin{matrix} \text{R} \\ \text{R}' \end{matrix}$
 (secondary amine)

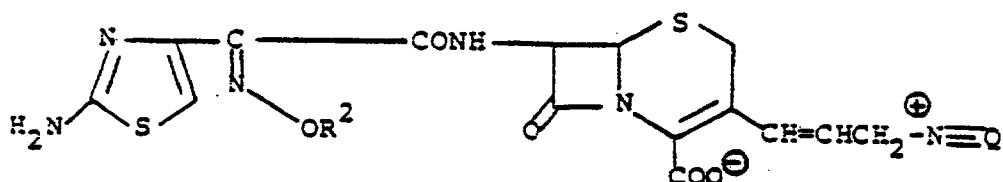


R''I



$\text{Q} \equiv \text{N}$
 (tertiary amine)

[reduction, when m = 1]
deblock

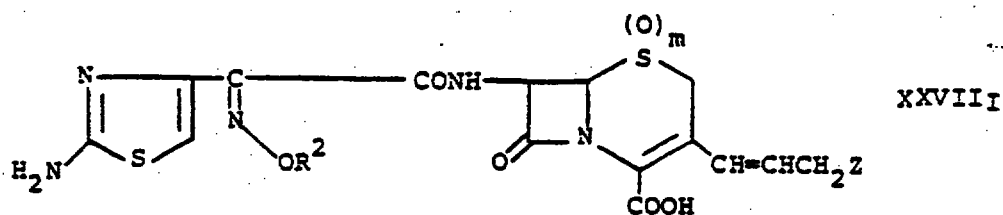


Reaction Scheme 1 shows two alternate means of going from Compound X to Compound XII. The direct route, utilizing a tertiary amine $Q \equiv N$, applicable for the preparation of all compounds of Formula I. The indirect route, via Compound XXIX, utilizes a secondary amine as reactant, and is quaternized in the following step. The secondary amine $RR'NH$ may be acyclic (e.g. dimethylamine) or cyclic (e.g. pyrrolidine), and this indirect procedure therefore is suitable for the preparation of compounds of Formula I in which the quaternary ammonio group is acyclic or "mixed" acyclic/cyclic. This indirect route is not suitable for the preparation of compounds of Formula I wherein the quaternary nitrogen is in a fully unsaturated heterocyclic ring (e.g. pyridinio, thiazolio, 2-amino-5-thiazolo[4,5-c]pyridinio, and the like):

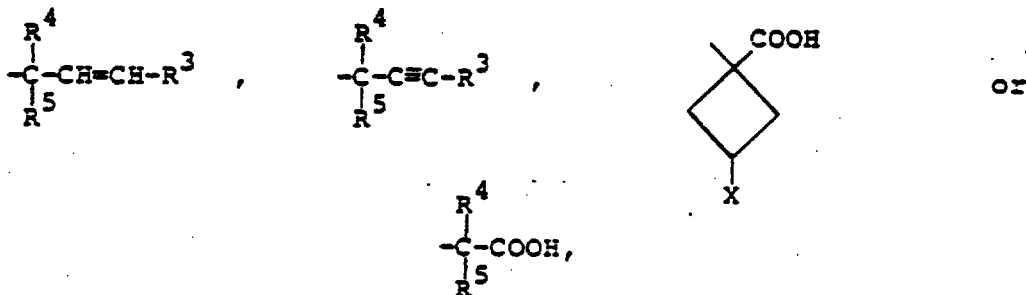
25

As used herein, the terms "(lower)alkyl" and "(lower)-alkoxy" mean straight or branched chain alkyl and alkoxy groups containing from 1 to 6 carbon atoms, inclusive.

According to the present invention, there are provided compounds of the formula



wherein Z is chloro, bromo or iodo, m is 0 or 1 and R² is hydrogen, a straight or branched chain alkyl group containing from 1 to 4 carbon atoms, or a group of the formula



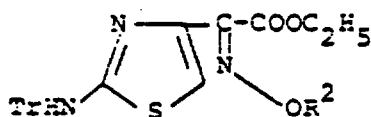
in which R³ is hydrogen, (lower)alkyl or carboxyl, X is halogen, hydroxy or (lower)alkoxy, and R⁴ and R⁵ are each independently

hydrogen, methyl or ethyl, or R^4 and R^5 , taken together with the carbon atom to which they are attached, may be a cycloalkylidene ring containing from 3 to 5 carbon atoms, and salts and esters thereof. Also included are compounds of Formula XXVIII in which the amino and/or carboxyl groups are protected by conventional amino-protecting or carboxyl-protecting groups.

A synthetical route affording these compounds, via precursors of the formulae VII and VIII, has already been indicated, in the foregoing "Reaction Scheme 1". More specific procedures will be found in the "Preparations" section which now follows.

(27)

Preparation No. 1



III

Ethyl (Z)-2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetate
(III-1)

A mixture of ethyl (Z)-2-hydroxyimino-2-(2-tritylaminothiazol-4-yl) acetate (II) (5.00 g, 10.9 mmoles), CH_3I (2.04 mL, 32.8 mmoles) and K_2CO_3 (4.54 g, 32.8 mmoles) in dry dimethylsulfoxide (DMSO) (100 mL) was stirred at room temperature overnight and then poured into water (250 mL). The precipitate which formed was collected by filtration, washed with water and dried to give the title compound (5.15 g, quantitative yield). Mp. 115°C (dec.).

NMR : δ^{CDCl_3} ppm 1.32 (3H, t), 3.98 (3H, s), 4.30 (2H, q), 6.42 (1H, s), 7.2 (1H, s), 7.25 (15H, s).

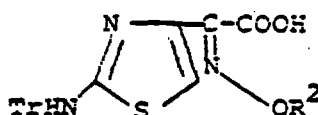
Compounds III-2, III-3, III-4', III-5', III-6' and III-7 were prepared by the general procedure set forth above, but replacing the methyl iodide with the appropriate iodide or bromide.

Compound	R^2 (or $\text{R}^{2'}$)	Yield (%)	Mp ($^\circ\text{C}$)	Literature
				Mp ($^\circ\text{C}$)
III-1	methyl	100	115 (dec.)	120 (dec.) ⁽¹⁾
III-2	ethyl	67	97-98	*
III-3	allyl	*	*	*
III-4'	$-\text{C}(\text{CH}_3)_2\text{COOtButyl}$	100	125-126	123.5-125 ⁽²⁾ ; 134 ⁽³⁾
III-5'	 COOtButyl	68	81-83	not reported ⁽³⁾
III-6'	 COOtButyl	36	75-85	(new compound)
III-7	$-\text{CH}_2\text{C}\equiv\text{CH}$	94	70-73	not reported ⁽⁴⁾

*The ester was hydrolyzed without isolation

- (1) Tetrahedron, 34, 2233 (1978)
- (2) U.S. Patent 4,258,041
- (3) U.S. Patent 4,288,434
- (4) U.S. Patent 4,294,960

Preparation No. 2



IV

(Z)-2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (IV-1)

The ethyl ester III-1 prepared in Preparation No. 1 (6.00 g, 12.7 mmoles) in ethanol (120 mL) was treated with 2N NaOH (12.7 mL) at room temperature overnight. The reaction mixture was adjusted to pH 8 by the addition of powdered dry ice and the solvent was evaporated under reduced pressure. The residue was dissolved in water (100 mL) and the solution was acidified with 1N HCl to pH 2 and then extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with a saturated aqueous NaCl solution, dried and evaporated. The residue was crystallized from ethyl acetate-hexane to afford 5.56 g (yield 98%) of the title product. Mp. 138-143°C (dec.).

NMR : δ ^{13}C ppm 3.89 (3H, s), 6.52 (1H, s), 7.2 (15H, s).

Compounds IV-2, IV-3, IV-4', IV-5', IV-6' and IV-7 were prepared by the general procedure set forth above.

Compound	R^2 (or $\text{R}^{2'}$)	Yield (%)	Mp (°C,	Literature
			dec.)	Mp (°C, dec.)
IV-1	methyl	98	138-143	ca. 140 ⁽¹⁾
IV-2	ethyl	85	140-145	not reported ⁽¹⁾
IV-3	allyl	66	170-178	ca. 170 ⁽¹⁾
IV-4'	$-\text{C}(\text{CH}_3)_2\text{COOtButyl}$	77	174-175	152-156 ⁽²⁾ ; 190 ⁽³⁾

29

Compound	R ² (or R ^{2'})	Yield (%)	Mp (°C, dec.)	Literature Mp (°C, dec.)
IV-5'	 COOtButyl	78	163-164	not reported ⁽³⁾
IV-6'	 COOtButyl	51	125-135	new compound
IV-7	-CH ₂ C≡CH	88	136-138	(4)

(1) Tetrahedron, 34, 2233 (1978)

(2) U.S. Patent 4,258,041

(3) U.S. Patent 4,288,434

(4) The corresponding NH₂ compound is described in U.S. Patent 4,294,960

Preparation No. 3

Benzhydryl 3-Hydroxymethyl-7-phenylacetamido-3-cephem-4-carboxylate

To a stirred suspension of phosphate buffer (pH 7, 162.5 mL) and wheat bran (20 g, dry) at room temperature was added 7-phenylacetamidocephalosporanic acid sodium salt (5 g, 12.1 mmoles) in one portion. The progress of the reaction was monitored by HPLC until the hydrolysis was complete (5 hours). The suspension was filtered to remove the wheat bran and the filtrate was cooled to 5-10°C for extractive esterification. To the cooled solution was added methylene chloride (32 mL) followed by a 0.5M solution of diphenyldiazomethane in methylene chloride (24 mL). The pH was then adjusted to 3.0 with 28% phosphoric acid. After 1 hour the reaction mixture was allowed to rise to 20°C. Heptane (56 mL) was slowly added and the resulting crystalline title product was recovered by filtration. Yield of the title product was 3.0 g (50%).

Preparation No. 4

Benzhydryl 7-Amino-3-chloromethyl-3-cephem-4-carboxylate (V)

To a slurry of PCl_5 (8.3 g, 40 mmol) in CH_2Cl_2 (100 mL) was added pyridine (3.2 g, 40 mmol) and the mixture was stirred for 20 minutes at 20°C . To the mixture was added benzhydryl 3-hydroxymethyl-7-phenylacetamido-3-cephem-4-carboxylate prepared in Preparation No. 3 (5.1 g, 10 mmol) with stirring at -40°C , in one portion. The mixture was stirred at -10°C for 15 minutes and allowed to stand at -10°C to -15°C for 7 hours. To the cooled solution (-20°C) was added propane-1,3-diol (10 mL) and the mixture was allowed to stand at -20°C for 16 hours and then at room temperature for 20 minutes with stirring. The resulting solution was washed with ice-water (2 x 20 mL) and saturated aqueous NaCl (10 mL), dried over MgSO_4 and concentrated in vacuo. The gummy residue (12 g) was dissolved in a mixture of CHCl_3 and n-hexane (2:1), and subjected to chromatography using a silica gel column (200 g) and the same solvent as eluant. Fractions containing the title compound were evaporated in vacuo and the residue triturated with n-hexane to give the title product (2.1 g, 51%), melting at $>110^\circ\text{C}$ (dec.).

IR : ν_{KBr} 3400, 2800, 1785, 1725 cm^{-1} .

UV : $\lambda_{\text{max}}^{\text{EtOH}}$ 265 nm ($E_{1\text{cm}}^{1\%}$ 160).

NMR : $\delta_{\text{ppm}}^{\text{DMSO-d}_6 + \text{CDCl}_3}$ 3.69 (2H, s), 4.43 (2H, s), 5.09 (1H, d, $J = 4.5\text{Hz}$), 5.24 (1H, d, $J = 4.5\text{Hz}$), 6.87 (1H, s), 7.3 (10H, m).

Preparation No. 5

Benzhydryl 3-Chloromethyl-7-[(Z)-2-methoxyimino-2-(2-trityl-aminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (VI-1)

Benzhydryl 7-amino-3-chloromethyl-3-cephem-4-carboxylate prepared in Preparation No. 4 (2.29 g, 5.52 mmoles) in CH_3CN (57 mL) was treated with bis(trimethylsilyl)acetamide (BSA, 4.09 mL, 16.6 mmoles) at room temperature for 50 minutes to give a clear solution. To the solution was added an acid chloride solution, which was prepared from (Z)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (IV-1) (2.04 g, 4.60 mmoles) and PCl_5 (1.15 g, 5.52 mmoles) in methylene chloride (20 mL). The mixture was stirred at room temperature for 30 minutes, poured into cold water (200 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with aqueous NaCl , dried and evaporated. The residual syrup (4 g) was chromatographed on a silica gel (150 g) column by eluting with 10:1 and 3:1 mixtures of toluene and ethyl acetate successively. The fractions containing the desired compound were combined and evaporated to afford 2.61 g (68%) of VI-1 as an amorphous powder.

NMR : δ^{CDCl_3} ppm 3.50 (2H, s), 4.02 (3H, s), 4.33 (2H, s), 4.98 (1H, d), 5.87 (1H, q), 6.65 (2H, s), 6.90 (1H, s), 7.3 (25H, m).

Preparation No. 6

Benzhydryl 3-Iodomethyl-7-[(Z)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (VII-1)

A mixture of the 3-chloromethyl derivative prepared in Preparation No. 5 (VI-1) (1.50 g, 1.79 mmoles) and NaI (1.34 g, 8.93 mmoles) in methyl ethyl ketone (30 mL) was stirred at room temperature for 1 hour. After evaporation of the solvent the residue was dissolved in ethyl acetate (100 mL) and washed

with water, aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and aqueous NaCl , dried and evaporated to give the title compound VII-1 (1.47 g, 89%) as an amorphous powder.

NMR : δ^{CDCl_3} ppm 3.55 (2H, ABq), 4.00 (3H, s), 4.25 (2H, s), 4.97 (1H, d), 5.80 (1H, q), 6.65 (1H, s), 6.90 (1H, s), 7.3 (25H, m).

Preparation No. 7

Benzhydryl 3-Chloromethyl-7-[(Z)-2-ethoxyimino-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-cephem-4-carboxylate (VI-2)

To a solution of (Z)-2-ethoxyimino-2-(2-tritylamino-thiazol-4-yl)acetic acid (IV-2) (1.095 g, 2.4 mmoles) in dichloromethane (20 mL) was added phosphorus pentachloride (500 mg). After stirring for 1 hour at room temperature, the mixture was added in one portion to an ice-cooled solution of Compound V (1.083 g, 2.4 mmoles) and BSA (1 mL) in dichloromethane (20 mL). After stirring for 0.5 hour the reaction mixture was poured into 10% aqueous NaHCO_3 (200 mL) and extracted with CHCl_3 (100 mL). The extract was washed with water, dried over MgSO_4 , and evaporated under reduced pressure. The residue was chromatographed on a silica gel column. Elution with CHCl_3 gave VI-2 as an amorphous powder, 1.76 g (86%).

NMR : δ^{CDCl_3} ppm 1.40 (3H, t, CH_2CH_3), 3.53 (2H, ABq, 2-H), 4.37 (2H, s, $-\text{CH}_2\text{Cl}$), 4.60 (2H, q, $-\text{CH}_2\text{CH}_3$), 4.90 (1H, d, 6-H), 5.89 (1H, d, 7-H), 6.88 (1H, s, thiazole-H), 6.91 (1H, s, benzhydryl-CH).

Preparation No. 8

Diphenylmethyl 7-[(Z)-2-Ethoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-2)

A mixture of VI-2 prepared in Preparation No. 7 (1.07 g, 1.25 mmoles) and NaI (562 mg, 2.75 mmoles) in acetone (20 mL) was stirred for 1 hour. The mixture was filtered and the filtrate was poured into water and extracted with ethyl acetate. The organic layer was washed successively with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$, water and saturated aqueous NaCl, dried over MgSO_4 and evaporated to give 1.04 g (89%) of Compound VII-2.

NMR : δ_{CDCl_3} ppm 3.55 (2H, q, 2-H), 4.27 (2H, s, CH_2I), 5.02 (1H, d, 6-H), 5.87 (1H, d, 7-H), 6.68 (1H, s, thiazole ring H), 6.93 (1H, s, benzhydryl-CH).

Preparation No. 9

Benzhydryl 7-[(Z)-2-Allyloxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-chloromethyl-3-cephem-4-carboxylate (VI-3)

To a suspension of Compound V (1.35 g, 3 mmoles) in methylene chloride (20 mL) was added BSA (1.1 mL, 4.5 mmoles), and the mixture was stirred for 30 minutes at room temperature to become a clear solution. A mixture of (Z)-2-allyloxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (IV-3) (1.40 g, 3.0 mmoles) and phosphorus pentachloride (690 mg, 3.3 mmoles) in methylene chloride (20 mL) was stirred for 15 minutes at room temperature and poured in one portion into the solution of the trimethylsilylated Compound V. The mixture was stirred for 20 minutes at room temperature and diluted with ethyl acetate (200 mL), washed with aqueous sodium bicarbonate and water, dried and evaporated under reduced pressure. The oily residue was purified by silica gel column chromatography (Wako-gel,

C-200, 30 g). The column was eluted with chloroform and the fractions containing the desired product were combined.

Evaporation under reduced pressure afforded the title compound (VI-3) as an amorphous powder, yield 2.32 g (89%). Mp. 100-115°C (dec.).

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3390, 1790, 1730, 1680, 1530, 1380, 1250, 1160, 1020.

NMR : δ^{CDCl_3} ppm 3.50 (2H, 2-H), 4.32 (2H, s, 3-CH₂), 4.6-6.1 (7H, m, CH₂CH=CH₂ and 6,7-H), 6.70 (1H, s, thiazole-H), 6.90 (1H, s, Ph₂CH), 7.1-7.6 (30H, m, phenyl protons).

Anal. Calc'd. for C₄₈H₄₀N₅O₅S₂Cl·1/3CHCl₃: C, 64.05; H, 4.45; N, 7.73; S, 7.08; Cl, 7.82.

Found: C, 64.13, 63.99; H, 4.61, 4.64; N, 7.50, 7.30; S, 6.85, 6.85; Cl, 7.55, 7.46.

Preparation No. 10

Benzhydryl 7-[(Z)-2-Allyloxyimino-2-(2-tritylaminothiazol-4-yl)-acetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-3)

A mixture of Compound VI-3 (2.30 g, 2.65 mmols) and sodium iodide (2 g, 13.3 mmols) in acetone (15 mL) was stirred for 1 hour at room temperature and then evaporated under reduced pressure. A solution of the oily residue in ethyl acetate (200 mL) was washed with 10% sodium thiosulfate and water, evaporated under reduced pressure to afford Compound VII-3 as an amorphous powder, which was used in the subsequent step without further purification. Yield 2.52 g (99%).

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Preparation No. 11

Benzhydryl 3-Chloromethyl-7-[(Z)-2-(2-t-butoxycarbonylprop-2-oxymino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (VI-4')

Procedure 1

A mixture of (Z)-2-(2-t-butoxycarbonylprop-2-oxymino)-2-(2-tritylaminothiazol-4-yl)acetic acid (IV-4') (1.94 g, 3.6 mmol) DCC (742 mg, 3.6 mmol) and N-hydroxybenztriazole (486 mg, 3.6 mmol) in tetrahydrofuran (THF) (45 mL) was stirred at room temperature for 45 minutes, during which dicyclohexylurea separated. The dicyclohexylurea was removed by filtration and the filtrate was mixed with V (1.5 g, 3.6 mmol). The mixture was stirred overnight at room temperature and then evaporated in vacuo. The residual oil was dissolved in CHCl_3 (20 mL), washed with saturated aqueous NaHCO_3 and saturated aqueous NaCl , dried over MgSO_4 and evaporated to dryness. The residue (3.9 g) was dissolved in n-hexane: CHCl_3 (1:2) and passed through a silica gel column (40 g) using the same solvent system. Fractions containing the title compound were evaporated in vacuo to give 1.3 g (39%) of VI-4' melting at $>100^\circ\text{C}$ (dec.).

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3390, 1790, 1715, 1690.

UV : $\lambda_{\text{max}}^{\text{EtOH}}$ nm 240 ($\epsilon_{\text{1}}^{1\%}$ 280), 265 ($\epsilon_{\text{1}}^{1\%}$ 190).

NMR : δ^{CDCl_3} ppm 1.45 (9H, s), 1.63 & 1.66 (6H, each s), 3.49 (2H, broad s), 4.34 (2H, s), 4.96 (1H, d, $J=4.5\text{Hz}$), 5.90 (1H, d-d, $J=4.5$ & 7.5), 6.66 (1H, s), 6.86 (1H, s), 7.0-7.5 (25H, m), 8.23 (1H, d, $J=7.5\text{Hz}$).

Procedure 2

A solution of V (1.86 g, 4.49 mmol) in CH₃CN (46.5 mL) was treated with BSA (3.33 mL, 13.5 mmol) at room temperature for 50 minutes to give a clear solution. To the solution was added an acid chloride solution which had been prepared from IV-4' (2.56 g, 4.49 mmol) and PCl₅ (1.12 g, 5.38 mmol) in methylene chloride (26 mL). The mixture was stirred at room temperature for 30 minutes, poured into cold water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with aqueous NaCl, dried and evaporated. The residual syrup (5 g) was chromatographed on a silica gel (100 g) column by eluting with 10:1 mixture of toluene and ethyl acetate. The fractions containing the desired compound were combined and evaporated to afford 2.84 g (55%) of VI-4'.

Preparation No. 12

Benzhydryl 7-[(2)-2-(2-t-Butoxycarbonylprop-2-oxymino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-4')

A mixture of VI-4' (500 mg, 0.53 mmol) and NaI (240 mg, 1.6 mmol) in acetone (3 mL) was stirred for 2 hours at room temperature and then evaporated in vacuo. To the residue were added CH₂Cl₂ (20 mL) and water (10 mL). The organic layer was washed with 10% w/v sodium thiosulfate (5 mL) and aqueous NaCl (5 mL), dried over MgSO₄ and evaporated to dryness to give 540 mg (99%) of VII-4' as an amorphous powder melting at 106°C (dec.).

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 3350, 1790, 1690.

UV : $\lambda_{\text{max}}^{\text{EtOH}}$ nm 240 ($\epsilon_1^{1\%}$ 270), 265 ($\epsilon_1^{1\%}$ 190).

NMR : δ^{CDCl_3} ppm 1.44 (9H, s), 1.65 (6H, s), 3.54 (2H, ABq), 4.28 (2H, s), 4.98 (1H, d, $J=4.5\text{Hz}$), 5.85 (1H, d-d, $J=4.5 \text{ \& } 7.5\text{Hz}$), 6.70 (1H, s), 6.90 (1H, s), 7.1-7.5 (25H, m).

Preparation No. 13

Diphenylmethyl 7-[(Z)-2-(1-t-Butoxycarbonylcyclobut-1-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-chloromethyl-3-cephem-4-carboxylate (VI-5')

Phosphorus pentachloride (1.46 g, 7 mmoles) was added to a suspension of (Z)-2-(1-t-butoxycarbonylcyclobut-1-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetic acid [IV-5'] (4.09 g, 7 mmoles) in 70 mL of dry methylene chloride, and the mixture was stirred for 1 hour at room temperature. The acid chloride solution was added at -20°C to a solution of silylated 7-ACA ester, which was prepared by adding BSA (5.6 mL, 21 mmoles) to a stirred suspension of benzhydryl 7-amino-3-chloromethyl-3-cephem-4-carboxylate hydrochloride [V] (3.16 g, 7 mmoles) in dry methylene chloride (70 mL). The mixture was stirred for 20 minutes at -10°C and then at room temperature for 40 minutes. The reaction mixture was evaporated and diluted with ethyl acetate (300 mL), and the organic layer was washed with 5% aqueous sodium bicarbonate, water and a saturated sodium chloride solution. After drying over sodium sulfate, the solvent was evaporated and the residue was purified by silica gel column chromatography (Wako gel C-200, 60 g); elution with chloroform. The fractions containing the desired product were combined and evaporated to obtain 5.88 g (86%) of VI-5' as a yellow powder.

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1790, 1725, 1690, 1525.

UV : $\lambda_{\text{max}}^{\text{EtOH}}$ nm 240 ($\epsilon_{1\text{ cm}}^{1\%} = 232$), 265 ($\epsilon_{1\text{ cm}}^{1\%} = 181$).

Preparation No. 14

Diphenylmethyl 7-[(2)-2-(1-t-Butoxycarbonylcyclobut-1-oxymino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-5')

To a stirred solution of VI-5' (5.4 g, 5.5 mmoles) in acetone (108 mL) was added sodium iodide (2.48 g, 16.5 mmoles), and the mixture was stirred at room temperature for 3 hours. The reaction mixture was then filtered and evaporated to dryness, and the residue was dissolved in ethyl acetate (200 mL). The solution was washed with water (100 mL), 10% w/v sodium thiosulfate (40 mL) and saturated sodium chloride (3 x 70 mL). After drying over magnesium sulfate, the solvent was removed under reduced pressure to give 5.38 g (91%) of VII-5' as a yellow powder.

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1790, 1725, 1690, 1525.

UV : $\lambda_{\text{max}}^{\text{EtOH}}$ nm 240 ($\epsilon_{1\text{ cm}}^{1\%} = 197$), 265 ($\epsilon_{1\text{ cm}}^{1\%} = 154$).

NMR : δ^{CDCl_3} ppm 1.45 (9H, s), 1.8-2.8 (6H, m), 3.52 (2H, ABq), 4.25 (2H, s), 4.98 (1H, d, J = 5.3Hz), 5.87 (1H, dd, J = 9 & 5.3Hz), 6.70 (1H, s), 6.88 (1H, s), 6.90 (1H, s), 7.28 (25H, s), 8.41 (1H, d, J = 9Hz).

Preparation No. 15

Diphenylmethyl 3-chloromethyl-7-[(2)-2-propargyloxymino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate [VI-7]

Phosphorus pentachloride (910 mg) was added to a solution

of (2)-2-propargyloxyimino-2-(2-tritylaminothiazol-4-yl)acetic acid (IV-7) (1.7 g, 3.6 mmoles) in dichloromethane (30 mL). After stirring for 1 hour at room temperature the mixture was added in one portion to an ice-cooled solution of (V) (1.98 g, 4.4 mmoles) and N,O-bis(trimethylsilyl)acetamide (1.5 mL) in dichloromethane (30 mL). After stirring for 1 hour, the reaction mixture was poured into 10% aqueous NaHCO_3 (300 mL) and extracted with ethyl acetate (300 mL). The extract was washed with water, dried over MgSO_4 and evaporated under reduced pressure. The residue was chromatographed on a silica gel column. Elution with CHCl_3 gave the title compound [VI-7] as an amorphous powder weighing 2.1 g (66%).

NMR : δ^{CDCl_3} ppm 2.45 (1H, t, CH), 3.53 (2H, d, 2- CH_2), 4.37 (2H, s, $-\text{CH}_2\text{Cl}$), 4.83 (2H, d, O- $\text{CH}_2\text{C}\equiv\text{CH}$), 5.03 (1H, d, 6-H), 5.90 (1H, q, 7-H), 6.70 (1H, s, thiazole-H), 6.92 (1H, s, benzhydryl-CH).

Preparation No. 16

Diphenylmethyl 7-[(2)-2-propargyloxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate [VII-7]

A mixture of diphenylmethyl 3-chloromethyl-7-[(2)-2-propargyloxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (VI-7) (2.0 g, 2.3 mmoles) and NaI (1.04 g, 6.9 mmoles) in acetone (40 mL) was stirred for 1 hour. The mixture was filtered and the filtrate was poured into water and extracted with ethyl acetate. The organic layer was washed with 5% aqueous $\text{Na}_2\text{S}_2\text{O}_3$, water and a saturated aqueous NaCl , successively. It was then dried over MgSO_4 and evaporated to give 2.2 g (98%) of the title compound [VII-7].

NMR : δ^{CDCl_3} ppm 2.45 (1H, t, CH), 3.53 (2H, d, 2- CH_2), 4.25 (2H, s, CH_2I), 4.83 (2H, d, O- CH_2), 5.0 (1H, d, 6-H), 5.80 (1H, q, 7-H), 6.70 (1H, s, thiazole-H), 6.92 (1H, s, benzhydryl-CH).

Preparation No. 17

Diphenylmethyl 7-[(2)-2-Methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-triphenylphosphoniomethyl-3-cephem-4-carboxylate Iodide (VIII-1)

A mixture of diphenylmethyl 7-[(2)-2-(2-tritylaminothiazol-4-yl)-2-methoxyiminoacetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-1, 7.8 g, 8.4 mmoles) and triphenylphosphine (4.4 g, 16.8 mmoles) in benzene (160 ml) was stirred at room temperature for 1 hour. The resulting precipitate was collected by filtration to afford 8.0 g of the title compound VIII-1. The mother liquor was concentrated and the residue was triturated with n-hexane to yield an additional amount (1.3 g) of VIII-1. Total yield 9.3 g (93%).

IR : $\nu_{\text{KBr max}}^{\text{cm}^{-1}}$ 1770, 1700, 1660, 1510.

Preparation No. 18

Diphenylmethyl 3-(3-Chloro-1-propen-1-yl)-7-[(2)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (IX-1)

The phosphonium iodide VIII-1 (20 g, 17 mmoles) in chloroform (130 ml) was shaken with aqueous sodium hydroxide (10 ml 2N NaOH plus 70 ml water) and the chloroform layer was washed with water and dried over sodium sulfate. To the chloroform solution was added chloroacetaldehyde (2 g, 25 mmoles) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was chromatographed on a silica gel column (200 g), eluted with toluene (1.5 L) and toluene-ethyl acetate (10:1). The desired fractions were combined and concentrated to yield 10.3 g (71%) of the title compound IX-1.

Rf : 0.34 (chloroform/ethyl acetate = 20/1; silica gel plate)

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IR : $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 1780, 1710, 1660, 1510.

NMR: $\delta^{\text{CDCl}_3+\text{D}_2\text{O}}$ ppm 3.53 (2H, s, 2-H), 3.96 (2H, d, 7 Hz, -CH₂Cl), 4.05 (3H, s, -OCH₃), 5.03 (1H, d, 4.5 Hz, 6-H), 5.87 (1H, d, 4.5 Hz, 7-H), 6.70 (1H, s, thiazole-H), 6.96 (1H, s, -CHPh₂), 7.30 (25H, s, phenyl-H).

Preparation No. 19

Diphenylmethyl 3-(3-Iodo-1-propen-1-yl)-7-[(2)-2-methoxyimino-2-(2-tritylaminothiazol-4-yl)acetamido]-3-cephem-4-carboxylate (X-1)

A mixture of the chloropropenyl derivative IX-1 (1.9 g, 2.3 mmoles) and sodium iodide (1.0 g, 6.9 mmoles) in acetone (40 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The ethyl acetate solution was washed with 10% aqueous sodium thiosulfate (50 ml) and aqueous sodium chloride (50 ml), dried over sodium sulfate and concentrated to give 2.0 g (94%) of the title compound X-1.

Rf : 0.34 (chloroform/ethyl acetate = 20/1; silica gel plate).

IR : $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 1770, 1710, 1660, 1500.

NMR: $\delta^{\text{CDCl}_3+\text{D}_2\text{O}}$ ppm 3.50 (2H, s, 2-H), 3.84 (2H, d, 7 Hz, -HC=CH-CH₂I), 4.03 (3H, s, -OCH₃), 5.05 (1H, d, 4.5 Hz, 6-H), 5.90 (1H, d, 4.5 Hz, 7-H), 6.75 (1H, s, thiazole-H), 6.98 (1H, s, -CHPh₂), 7.30 (25H, s, phenyl-H).

Preparation No. 20

Diphenylmethyl 7-[(Z)-2-(2-t-Butoxycarbonyl-2-propoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-triphenylphosphoniomethyl-3-cephem-4-carboxylate Iodide (VIII-4')

A mixture of diphenylmethyl 7-[(Z)-2-(2-t-butoxy-

carbonyl-2-propoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-4', 5.3 g, 5 mmols) and triphenylphosphine (2.6 g, 10 mmols) in benzene (100 ml) was stirred at room temperature for 1 hour and diluted with diisopropyl ether. The resulting precipitate was collected by filtration to yield 6.0 g (91%) of the title compound VIII-4'.

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1780, 1705, 1670, 1500.

Preparation No. 21

Diphenylmethyl 7-[(2)-2-(2-t-Butoxycarbonyl-2-propoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(3-chloro-1-propen-1-yl)-3-cephem-4-carboxylate (IX-4')

The phosphonium iodide (VIII-4', 5.7 g, 4.3 mmols) in chloroform (100 ml) was treated with aqueous sodium hydroxide (0.34 g NaOH in 100 ml of water) at room temperature. The mixture was washed with water (150 ml) and dried over sodium sulfate. To the chloroform solution was added chloroacetaldehyde (0.5 g, 6.5 mmols) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was chromatographed on a silica gel column (120 g), eluted with benzene (500 ml) and benzene-ethyl acetate (10:1). The desired fractions were combined and concentrated to yield 2.6 g (61%) of IX-4'.

Rf : 0.18 (benzene/ethyl acetate = 20/1; silica gel plate).

IR : $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} 1785, 1720, 1690, 1520.

UV : $\lambda_{\text{max}}^{\text{EtOH}}$ nm(ϵ) 240 (sh, 23400), 278 (16000).

Preparation No. 22

Diphenylmethyl 7-[(2)-2-(2-t-Butoxycarbonyl-2-propoxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(3-iodo-1-propen-1-yl)-3-cephem-4-carboxylate (X-4')

A mixture of the chloropropenyl derivative IX-4' (2.4 g, 2.4 mmoles) and sodium iodide (1.1 g, 7.2 mmoles) in acetone (50 ml) was stirred at room temperature for 1 hour. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (50 ml). The ethyl acetate solution was washed with 10% aqueous sodium thiosulfate (50 ml), water (50 ml) and aqueous NaCl solution (50 ml), dried over sodium sulfate and concentrated to yield 2.4 g (93%) of X-4'.

IR : $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 1775, 1710, 1670, 1500.

Preparation No. 23

Diphenylmethyl 7-[(2)-2-(1-t-Butoxycarbonylcyclobut-1-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-triphenylphosphonio-methyl-3-cephem-4-carboxylate Iodide (VIII-5')

A mixture of diphenylmethyl 7-[(2)-2-(1-t-butoxycarbonylcyclobut-1-oxyimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-iodomethyl-3-cephem-4-carboxylate (VII-5', 6.4 g, 6 mmoles) and triphenylphosphine (2.4 g, 9 mmoles) in benzene (120 ml) was stirred at room temperature for 2 hours and diluted with n-hexane (ca. 500 ml). The resulting precipitate was collected by filtration to afford 7.5 g (94%) of the title compound VIII-5'.

IR : $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 1780, 1710, 1670, 1510.

Preparation No. 24

Diphenylmethyl 7-[(2)-2-(1-t-Butoxycarbonvicyclobut-1-oxvimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(3-chloro-1-propen-1-yl)-3-cephem-4-carboxylate (IX-5')

The phosphonium iodide VIII-5' (7.4 g, 5.5 mmoles) in chloroform (150 ml) was treated with aqueous sodium hydroxide (0.44 g NaOH in 150 ml of water) at room temperature. The mixture was washed with water and dried over sodium sulfate. To the chloroform solution was added chloroacetaldehyde (863 mg, 11 mmoles) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated in vacuo and the residue was chromatographed on a silica gel column (150 g), eluted with benzene (500 ml) and benzene-ethyl acetate (10:1). The desired fractions were combined and concentrated to give 2.95 g (53%) of the title compound IX-5'. M.p. >110°C (dec.).

R_f : 0.61 (chloroform/ethyl acetate = 20/1; silica gel plate).

IR : $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 1780, 1720, 1685, 1520.

UV : $\lambda_{\text{max}}^{\text{EtOH}} \text{ nm}(\epsilon)$ 240 (24700), 296 (15200).

Preparation No. 25

Diphenylmethyl 7-[(2)-2-(1-t-Butoxycarbonvicyclobut-1-oxvimino)-2-(2-tritylaminothiazol-4-yl)acetamido]-3-(3-iodo-1-propen-1-yl)-3-cephem-4-carboxylate (X-5')

A mixture of the chloropropenyl derivative IX-5' (3.5 g, 3.5 mmoles) and sodium iodide (1.0 g, 7.0 mmoles) in acetone (70 ml) was stirred at room temperature for 1 hour. After evaporation of the solvent, the residue was dissolved in ethyl acetate (100 ml) and the solution was washed with 10% aqueous sodium thiosulfate (100 ml) and aqueous NaCl solution (100 ml), dried over sodium sulfate and concentrated under reduced pressure to

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afford 3.3 g (86%) of X-5'.

IR : $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$ 1780, 1720, 1680, 1520.

UV : $\lambda_{\text{max}}^{\text{EtOH}} \text{ nm}(\epsilon)$ 308 (17900).

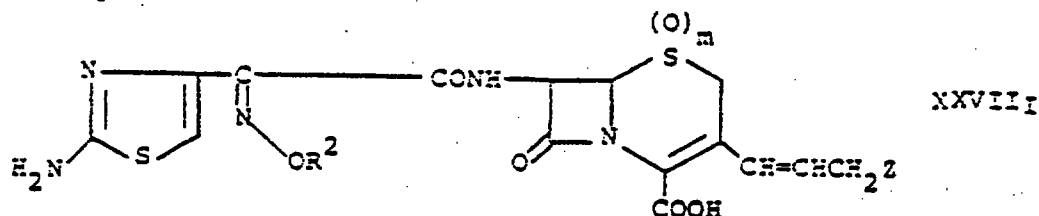
For specific Examples dealing with the preparation of compounds of the Formula I, the reader is referred to the specification of our primary Application No.84.03474 (2134522).



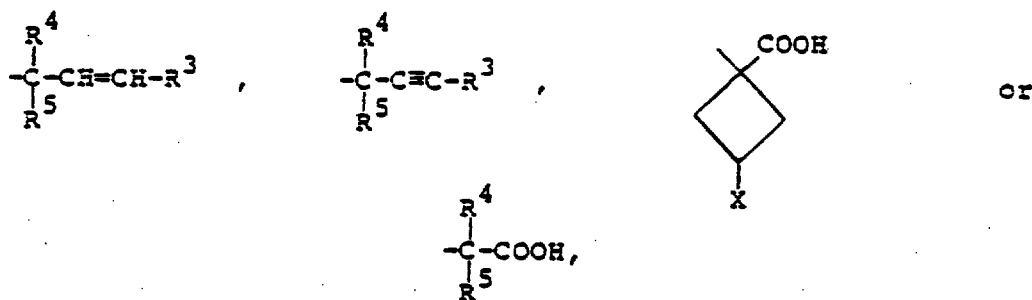
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CLAIMS

1. A compound of the formula



wherein Z is chloro, bromo or iodo, m is 0 or 1 and R² is hydrogen, a straight or branched chain alkyl group containing from 1 to 4 carbon atoms, or a group of the formula



in which R³ is hydrogen, (lower)alkyl or carboxyl, X is halogen, hydroxy or (lower)alkoxy, and R⁴ and R⁵ are each independently hydrogen, methyl or ethyl, or R⁴ and R⁵, taken together with the carbon atom to which they are attached, may be a cycloalkylidene ring containing from 3 to 5 carbon atoms, a salt or ester thereof, or an amino-protected, carboxyl-protected or amino- and carboxyl-protected derivative thereof.

2. A compound of Claim 1 in which R² is methyl.
3. A compound of Claim 1 in which R² is 2-carboxyprop-2-yl.
4. A compound of Claim 1 in which R² is 1-carboxycyclobut-1-yl.
5. The compound of Claim 1 which is diphenylmethyl 3-(3-iodo-1-propen-1-yl)-7-[(2)-2-methoxyimino-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-cephem-4-carboxylate.



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6. The compound of Claim 1 which is diphenylmethyl 7-
[(Z)-2-(2-t-butoxycarbonyl-2-propoxyimino)-2-(2-tritylamino-
thiazol-4-yl)acetamido]-3-(3-iodo-1-propen-1-yl)-3-cephem-4-
carboxylate.

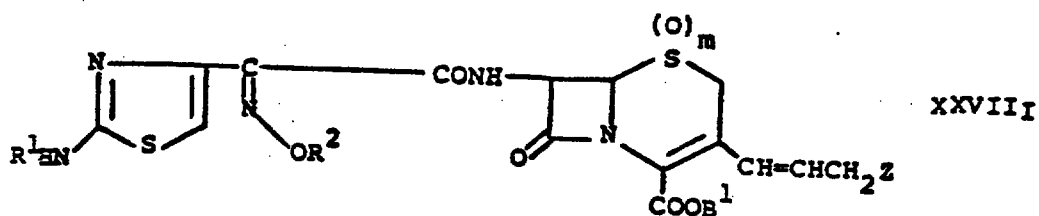
7. The compound of Claim 1 which is diphenylmethyl 7-
[(Z)-2-(1-t-butoxycarbonylcyclobut-1-oxyimino)-2-(2-tritylamino-
thiazol-4-yl)acetamido]-3-(3-iodo-1-propen-1-yl)-3-cephem-4-
carboxylate.

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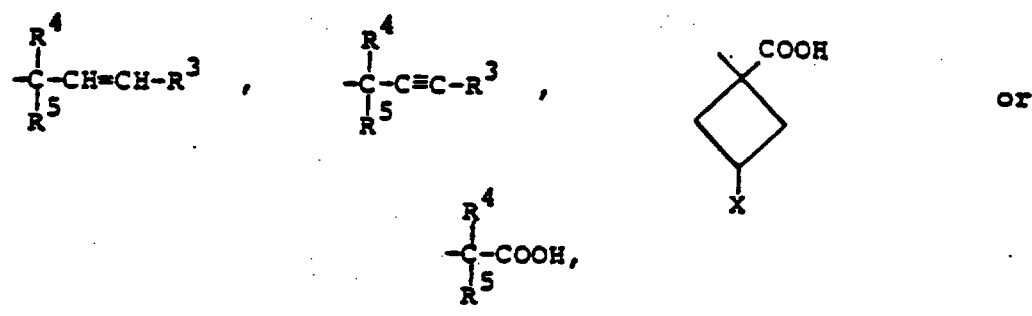
8. A process for the preparation of compounds of the formula



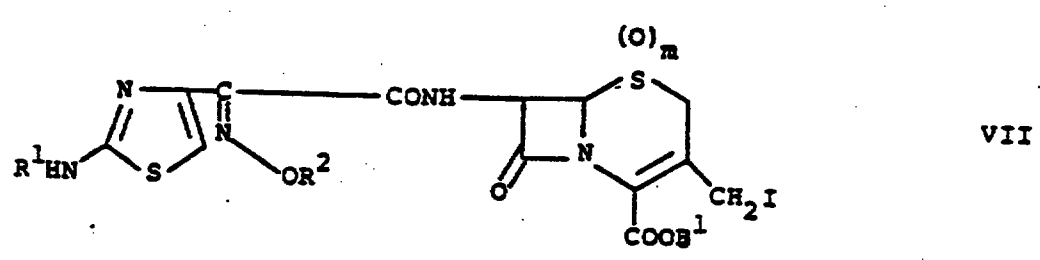
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wherein B¹ is hydrogen or a carboxyl-protecting group, Z is chloro, bromo or iodo, m is 0 or 1, R¹ is hydrogen or an amino-protecting group, and R² is hydrogen, a straight or branched chain alkyl group containing from 1 to 4 carbon atoms, or a group of the formula

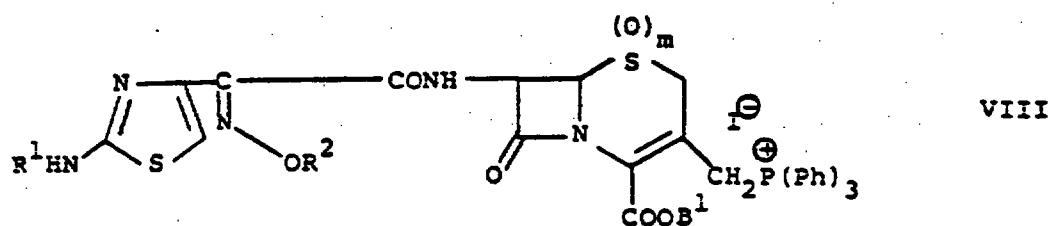


in which R³ is hydrogen, (lower)alkyl or carboxyl, X is halogen, hydroxy or (lower)alkoxy, and R⁴ and R⁵ are each independently hydrogen, methyl or ethyl, or R⁴ and R⁵, taken together with the carbon atom to which they are attached, may be a cycloalkylidene ring containing from 3 to 5 carbon atoms, and salts and esters thereof, which comprises a reacting compound of the formula VII

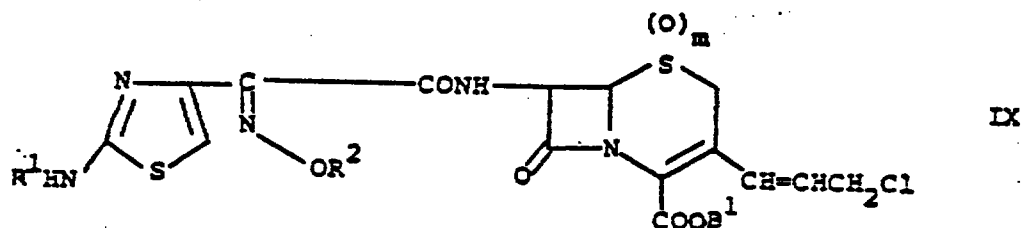




with $P(Ph)_3$ to give a compound of the formula VIII,



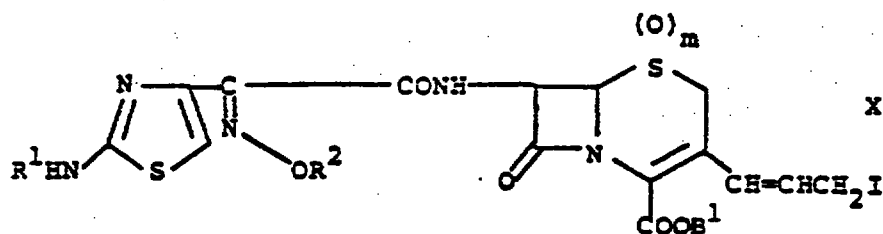
reacting compound VIII with base and $ClCH_2CHO$ to give a compound of the formula IX,



and, if m is 1, reducing the sulfoxide,

and subsequently removing all protecting groups,

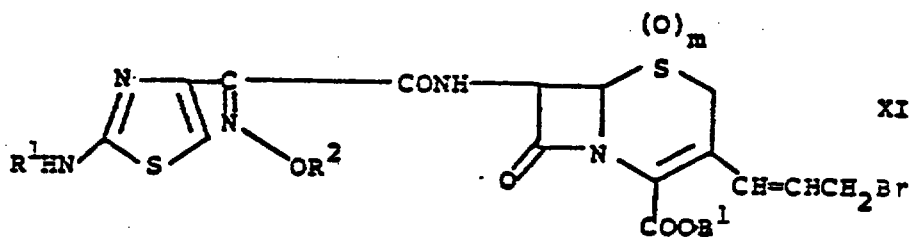
or further reacting compound IX with NaI or NaBr to give compound X or XI



or



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and if m is 1, reducing the sulfoxide of X or XI,
and subsequently removing all protecting
groups, and further converting them, if
desired to their pharmaceutically acceptable non-toxic salt or
their ester thereof.

9. The process of Claim 8, wherein R² is methyl, 2-
carboxyprop-2-yl or 1-carboxycyclobut-1-yl.

10. The process of Claim 8, characterized in that the
compounds a - c or their non-toxic salt or their ester thereof
are manufactured:

a) diphenylmethyl 3-(3-iodo-1-propen-1-yl)-7-[(Z)-2-
methoxyimino-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-
cephem-4-carboxylate,

b) diphenylmethyl 7-[(Z)-2-(2-t-butoxycarbonyl-2-
propoxyimino)-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-
(3-iodo-1-propen-1-yl)-3-cephem-4-carboxylate, and

c) diphenylmethyl 7-[(Z)-2-(1-t-butoxycarbonylcyclobut-1-
oxyimino)-2-(2-tritylamino-thiazol-4-yl)acetamido]-3-(3-iodo-1-
propen-1-yl)-3-cephem-4-carboxylate.



11. A process as claimed in claim 8, substantially as described
in any of the foregoing Preparations..

12. A compound as claimed in claim 1, prepared by a process
as claimed in claim 8, 9, 10 or 11.
