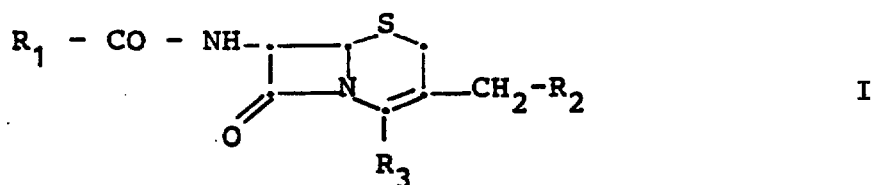


INTERMEDIARY PRODUCTS OF CEPHALOSPORINE, PREPARATION
PROCESS THEREOF AND UTILIZATION THEREOF

The invention relates to a process for the preparation of cephalosporine intermediate products of formula



wherein R_1 denotes the group of formula



R_2 denotes hydrogen, the acetoxy, the carbamoyloxy, a S-Y- group, whereby Y signifies an unsubstituted or substituted heterocycle, or R_2 denotes an optionally substituted pyridinium of formula



whereby R_8 and R_9 are the same or different and each denotes hydrogen, halogen, alkyl, hydroxy, carboxamido, alkoxy carbonyl, amino, monoalkylamino or dialkylamino, or together signify an

optionally substituted, 5- or 6-membered carbocyclic ring, and R_3 signifies the carboxyl, the carboxylate or a carboxylic acid ester group, and their use.

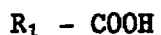
Valuable cephalosporin antibiotics can be prepared from the intermediary products of cephalosporine of formula I.

In these compounds, R_2 can be hydrogen. It can also be carbamoyloxy. Preferably it signifies acetoxy, -S-Y- or optionally substituted pyridinium. Suitable heterocycles as Y are known. Preferred heterocycles are for example thiadiazolyl, diazolyl, triazolyl, tetrazolyl, thiazolyl, thiatriazolyl, oxazolyl, oxadiazolyl, triazolylpyridyl, purinyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazolyl and triazinyl. These heterocycles may be unsubstituted or for example up to tri-substituted. Suitable substituents include (C_{1-4}) alkyl, (C_{1-4}) alkoxy, halogen, trihalo- (C_{1-4}) alkyl, hydroxy, oxo, mercapto, amino, carboxyl, carbamoyl, di- (C_{1-4}) alkylamino, carboxymethyl, carbamoylmethyl, sulphomethyl and methoxycarbonylamino. Heterocycles, indicated in the prior art to be particularly preferred include tetrazolyl, in particular 1-methyl-1H-tetrazol-5-yl, and triazinyl, in particular 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-as-triazin-3-yl, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl or 1,4,5,6-tetrahydro-4-methyl-5,6-dioxo-as-triazin-3-yl. Preferably R_2 is acetoxy, 1-methyl-1H-tetrazol-5-ylthio, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-ylthio or pyridinium.

As is known in the cephalosporin field, the compounds may be in the form of free acids ($R_3 = COOH$) or of salts, for example alkali- and alkaline earth - metal salts, preferably alkali metal salts, such as sodium salts. Furthermore, the compounds can also be in the form of esters, for example in the form of the pivaloyloxymethyl ester, but also as other esters, for example

acetoxymethyl, 1-acetoxyethyl, 1-ethoxycarbonyloxyethyl, 5-indanoyl or preferably hexanoylmethyl, phthalidyl, carbethoxymethoxymethyl or 3-carbethoxy-1-acetonyl ester. If R_2 denotes an optionally substituted pyridinium group, the compounds of formula I can also exist as inner salts. Further R_2 groups which contain basic radicals can similarly exist in the form of salts.

As already mentioned, the cephalosporin antibiotics which can be prepared from the compounds of formula I are known, and various methods for their preparation have already been proposed. One of these methods involves the acylation of the corresponding, optionally protected 7-aminocephalosporanic acid derivative with an active derivative of an acid of formula



A

wherein R_1 is defined as above.

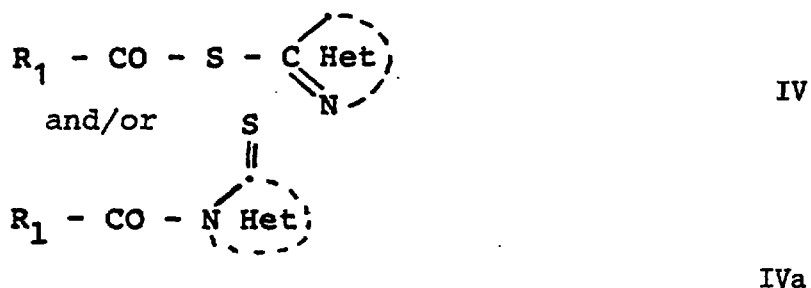
The various active derivatives that have been proposed also include active esters.

A difficulty that arises in the preparation of the compounds of formula I is that in practice it is essential to protect the amino substituent in the thiazolyl ring of the side-chain prior to the activation of the acid function, since otherwise competing reactions may lead to greatly reduced yields of the final product. The introduction, however, of protecting groups prior to the acylation step and their subsequent removal usually leads to reduced yields and purity of the final product, and considerably increases the reaction time, energy, effort and costs.

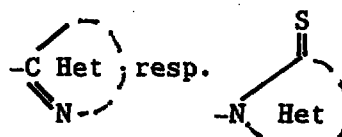
The present invention includes a process for the preparation of the desired compounds of formula I in high yield and purity,

without having to protect the amino substituent in the thiazolyl ring of the side-chain.

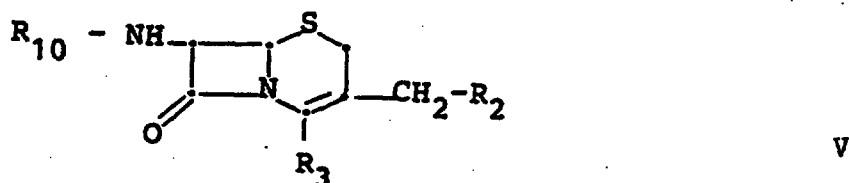
In particular the present invention includes a process for the preparation of compounds of formula I and their salts, characterised by reacting a compound of formula



wherein R_1 is defined as above, and



denote a 5- or 6-membered heterocycle, which may contain in addition to the N-atom one or two further heteroatoms, for example O, N and S, and which may be substituted or anellated with an optionally substituted benzene ring, with a compound of formula



wherein R_2 and R_3 are defined as above, and R_{10} denotes hydrogen or an amino protecting group, and if desired, deprotecting a

final product obtained and optionally converting a final product obtained, in which R_3 denotes COOH , into a salt, or vice versa.

The compounds of formula IV can also exist in the form of formula IVa, whereby the relation of the two forms to one another is dependent on the reaction components and the reaction conditions. If compounds having the structure of formula IV are indicated, these always also include compounds having the structure of formula IVa.

The process according to the invention is preferably effected in an inert solvent or in a mixture of such a solvent with water, e.g. in a chlorinated hydrocarbon such as dichloromethane, or in an acid ester such as ethyl acetate, or in acetone, dimethylformamide or dimethyl sulfoxide, at a temperature of -40 to $+60^\circ \text{C}$, especially at -15 to $+25^\circ \text{C}$, and advantageously at 0 to 20°C . The duration of the reaction is approximately $\frac{1}{2}$ to 48 hours. The reactants of formula IV and V are either employed in stoichiometric quantities, or an excess of up to 25% of the compound of formula IV is employed.

For the preparation of compounds of formula I in which R_3 signifies COOH , as well as their salts, the carboxyl group in the starting product of formula V can be protected. Suitable protecting groups are known and include not only those defined above, but also silyl ester protecting groups, especially the trimethylsilyl protecting group, which may be introduced e.g. by reaction of the free acid with N,O-bis(trimethylsilyl)acetamide.

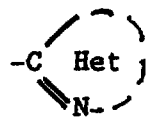
The 7-amino group of the starting material of formula V may also be protected. Suitable protecting groups are well-known and include e.g. the trimethylsilyl group, which may for example be introduced simultaneously when protecting of the carboxyl group.

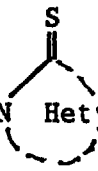
The amino substituent in the starting material IV/IVa may be in free or in protected form. As already mentioned, in general protection is not necessary. If protection is nevertheless desired, this may be effected in known manner, employing suitable known protecting groups.

After reaction of the compounds of formula IV and V, subsequent deprotection reactions may be effected in known manner. Likewise, conversion of the free acid form ($R_3 = \text{COOH}$) into the salts can be effected by known methods.

The final products may be isolated and purified by known methods.

In the process of the invention, heterocyclic thioesters are employed as a reactive derivative of the acid of formula A. It has been surprisingly found that these esters may be prepared and employed. Furthermore, it has been surprisingly found that an amino group present in the heterocycle of these esters does not lead to self-reaction. Accordingly, protection of this amino group in the subsequent acylation is not necessary. On the other hand, the amino group can of course be protected if this is desirable for another reason.

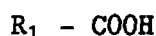
In the compounds of formula IV, the nature of the ring 

resp.  is not critical. The preferred compounds are

determined on the basis of factors such as ease of preparation and availability of starting material. The ring is preferably 2-pyridyl or in particular 2-benzothiazolyl. It can also be pyrimidinyl, triazolyl or thiazolyl.

The compounds of formula IV may be obtained by esterification of

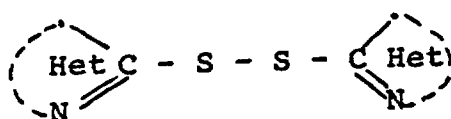
compounds of formula



VI

wherein R_1 is defined as above.

Esterification may be effected for example by reaction with a compound of formula



VII

wherein both $\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \\ \text{N} \end{array} \text{Het}$ are the same and are defined as above.

This esterification is preferably effected in the presence of a tri(lower alkyl)- or tri(aryl) phosphine or -phosphite, especially triphenylphosphine, and preferably at a temperature of -30 to $+50^\circ\text{C}$, especially -20 to $+25^\circ\text{C}$, and advantageously -5 to $+5^\circ\text{C}$. The solvent employed is an inert, non-hydroxy-containing organic solvent, e.g. a chlorinated hydrocarbon, such as dichloromethane. Where a compound of formula IV is desired, in which in R_1 the amino group is protected, the amino protecting group may be introduced prior to or subsequent to the esterification. The final products can be crystallised by treatment with lower alcohols and purified, whereby care must be taken that the temperature does not exceed 20°C , preferably 0°C .

As already mentioned, the compounds of formula I are intermediate products for the preparation of known antibiotics. These exhibit inhibiting activity against bacteria, as can be shown in investigations in vitro using the series dilution test

and in vivo in tests on mice, using various strains, e.g. of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus faecalis*, *Escherichia coli*, *Proteus vulgaris*, *Proteus mirabilis*, *Proteus morganii*, *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, *Alcaligenes faecalis*, *Klebsiella aerogenes*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Salmonella Heidelberg*, *Salmonella typhimurium*, *Salmonella enteritidis* and *Neisseria gonorrhoeae*. This inhibiting activity was established from a concentration of ca. 0.01 to 50 µg/ml resp. from a dosage of ca. 0.1 to 100 mg/kg body weight.

These cephalosporin antibiotics can therefore be used as antibacterially active antibiotics. For this use, the dosage to be administered depends on the compound used and the mode of administration, as well as the nature of the treatment. Satisfactory results are obtained by administering a daily dosage of ca. 1 to 6 g. If necessary, this amount can be administered in correspondingly smaller doses of 0.25 to 3 g two to four times daily, or in sustained release form.

The compounds in which R₃ denotes carboxyl can be used in the form of the free acids or their physiologically acceptable salts, whereby the salts have the same order of activity as the free acids. Suitable salt forms are for example alkali- and alkaline earth-metal salts, preferably alkali metal salts, especially sodium salts. The compounds can be administered together with inorganic or organic, pharmacologically inert diluents or carriers resp. adjuvants. They are employed for example as an ingredient of capsules, injection or instillation preparations.

In the following examples which illustrate the invention more fully but in no way limit its scope, all temperatures are given in degrees centigrade.

Example 1: 7-[[[(2-Amino-4-thiazolyl)-2-oxacetyl]amino]-3-[[[(1-methyl-1H-tetrazol-5-yl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid:

3.29 g of 7-amino-3-[(1-methyl-1H-tetrazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid are suspended in 25 ml of dichloromethane and treated with 2.7 ml of N,O-bis-(trimethylsilyl)acetamide. After 15 minutes, a clear solution results. This is cooled to -15°, and 3.9 g of 2-(2-aminothiazol-4-yl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester are added. After stirring for four hours at -15°, the preparation is stirred into 100 ml of ethanol, whereby the end product precipitates. This is stirred for one hour at 0°, filtered, washed with ethanol and vacuum dried. Yield: 3.9 g, i.e. 80.7%. M.p.: from 145° (decomp.). IR: 3350 N-H, 1800 C=O (β-lactam), 1690 C=O (amide), 1545 (amide II)

Example 2: 7-[[[(2-Amino-4-thiazolyl)-2-oxoacetyl]amino]-3-(1-pyridinium)-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-2-carboxylic acid. chloride:

3.28 g of 7-amino-3-(1-pyridiniummethyl)ceph-3-em-4-carboxylic acid. chloride are suspended in 25 ml of dichloromethane, and treated with 3 ml of N,O-bis-(trimethylsilyl)acetamide. After 10 minutes, a clear solution results. This is cooled to -15°, and 3.9 g of 2-(2-aminothiazol-4-yl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester are added. After stirring for four hours at -15°, the preparation is stirred into 100 ml of ethanol, whereby the end product precipitates. This is stirred for one hour at 0°, filtered, washed with ethanol and vacuum dried. Yield: 4.0 g, i.e. 83.0%. M.p.: from 162° (decomp.). IR: NH 3300 (broad), 1765, C=O (β-lactam), 1645, C=O (amide),

1610, (amide II).

Example 3: 7-[[(2-Amino-4-thiazolyl)-2-oxoacetyl]amino]-3-acetoxymethylceph-3-em-4-carboxylic acid:

5.44 g of 7-amino-3-acetoxymethylceph-3-em-4-carboxylic acid are suspended under a nitrogen atmosphere in 50 ml of dry dichloromethane, and treated with 5.4 ml of N,O-bis(trimethylsilyl)-acetamide. The preparation is stirred at room temperature until a clear solution results, and then cooled to -15°. 8.4 g of 2-(2-amino-4-thiazolyl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester are added and stirred for two hours at -15° and then for two hours at 0°. The solvent is carefully removed on a Rotavapor and the oily residue is triturated with 50 ml of ethanol, whereby the title compound precipitates. 6.3 g are obtained in the form of a yellow powder.

IR: 3335 NH, 1800 c=O (β -lactam), 1755 c=O, 1685 c=O (amide), 1515 (amide II)

Example 4: 7-[[(2-Amino-4-thiazolyl)-2-oxoacetyl]amino]-3-methylceph-3-em-4-carboxylic acid:

4.28 g of 7-amino-3-methylceph-3-em-4-carboxylic acid are suspended under a nitrogen atmosphere in 80 ml of dry dichloromethane, and mixed with 5.4 ml of N,O-bis(trimethylsilyl)acetamide. The preparation is stirred at room temperature until a clear solution results, and then cooled to -15°. 8.4 g of 2-(2-amino-4-thiazolyl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester are added and stirred for one hour at -15°, one hour at 0° and then two hours at +20°. The solvent is carefully removed on a Rotavapor and the oily residue is triturated with 50 ml of ethanol. The resulting deposit is filtered, washed with ethanol

and ether, and vacuum dried at 40°. 5.3 g of the title compound are obtained as a yellow powder.

IR: 3340 NH, 1790 c=o (β -lactam), 1685 c=o, 1540 (amide II).

Example 5: 7-[[[(2-Amino-4-thiazolyl)-2-oxoacetyl]amino]-3-(1,2,3-triazol-5-ylthiomethyl)ceph-3-em-4-carboxylic acid:

6.26 g of 7-amino-3-(1,2,3-triazol-5-ylthiomethyl)ceph-3-em-4-carboxylic acid are converted into the silyl ester in 50 ml of dichloromethane by adding 5.4 ml of N,O-bis(trimethylsilyl)acetamide. The mixture is cooled to -15°, and 10.1 g of 2-(2-amino-4-thiazolyl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester are added in the form of the tetrahydrofuran solvate. After two hours at -15° and one hour at 0°, the dichloromethane is removed on a Rotavapor, and the residue is stirred with 100 ml of methanol. The deposit is isolated in known manner. 8.4 g of the title compound are obtained as a yellow powder.

IR: 3320 NH (broad), 1790 c=o (β -lactam, 1680 c=o, 1530 (amide II)

Example 6: 7-[[[(2-Amino-4-thiazolyl)-2-oxoacetyl]amino]-3-[(2,3-cyclopenteno-1-pyridinium)methyl]ceph-3-em-4-carboxylate

9.88 g of 7-amino-3-[(2,3-cyclopenteno-1-pyridinium)methyl]-ceph-3-em-4-carboxylate. hydroiodide. monohydrate are silylated in 100 ml of dichloromethane with 11.4 ml of N,O-bis(trimethylsilyl)acetamide. The resulting solution is cooled to -15° and treated with 8.4 g of 2-(2-amino-4-thiazolyl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester. Stirring is effected for three hours at -15° and then 100 ml of ethanol and 3 ml of triethylamine are

added. The preparation is stirred for one hour at 0°, the resulting precipitate is filtered off, washed and dried. 11.5 g of the title compound are obtained as an orange powder.

IR: 3300 NH, 2965 CH₂, 1795 c=O (β-lactam), 1690 c=O, 1635 (amide I), 1545 (amide II).

Example 7: 7-[[[(2-Amino-4-thiazolyl)-2-oxoacetyl]amino]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)-thiomethyl]ceph-3-em-4-carboxylic acid:

14.85 ml of N,O-bis(trimethylsilyl)acetamide are added at 30° to 7.4 g of 7-amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]ceph-3-em-4-carboxylic acid (water content: 3.7%) in 50 ml of dichloromethane. After two hours at 30°, the mixture is cooled to -15°. 8.1 g of 2-(2-amino-4-thiazolyl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester are added, and stirred for six hours at -15°. The preparation is added to 500 ml of ethanol which has been warmed to 50°, then cooled whilst stirring and stirred for one hour at 0°. The deposit is filtered off, washed and dried. 9.1 g of the title compound are obtained as a yellow powder.

IR: 3320 NH, 1805 c=O, 1735 c=O, 1690 c=O, 1645 (amide I), 1555 (amide II).

PREPARATIONS OF STARTING COMPOUNDS IV

Example 8: 2-(2-Aminothiazol-4-yl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester

34.4 g of aminothiazolylglyoxylic acid are suspended in 500 ml of dichloromethane, and treated whilst stirring with 28 ml of triethylamine. The mixture is cooled to -15° and 64 g of

triphenylphosphine and 80 g of bisbenzothiazol-2-yl-disulfide are added. After stirring for two hours at -15° , the orange deposit is filtered off, washed with cold dichloromethane and vacuum dried. Yield: 57.7 g, i.e. 89.8%.

IR: 3300 N-H, 1675 carbonyl (thioester), 1645 carbonyl (amide), 1540 amide bands.

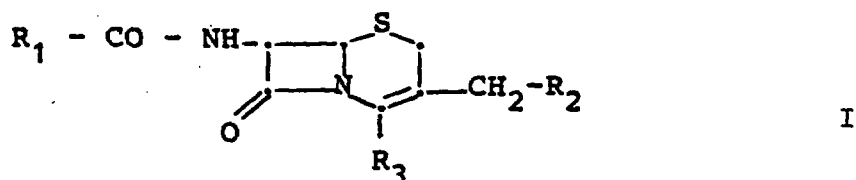
Example 9: 2-(2-Aminothiazol-4-yl)-2-oxothioacetic acid (S-benzothiazol-2-yl)ester:

80 g of bisbenzothiazol-2-yl-disulfide and 64 g of triphenylphosphine are suspended in 500 ml of tetrahydrofuran and cooled to -15° . 34.4 g of aminothiazolyglyoxylic acid are added, and 16.1 ml of pyridine are added slowly in drops, such that the internal temperature does not exceed -15° . The orange suspension is stirred for two hours at -15° . the deposit is filtered off, washed with cold tetrahydrofuran and vacuum dried.

Yield: 62.2 g as tetrahydrofuran solvate. M.p.: at 80° evolution of THF, from 123° (decomp.). THF content (by gas chromatography): 17%.

CLAIMS:

1. Process for the preparation of cephalosporine intermediate products of formula



wherein R_1 denotes the group of formula

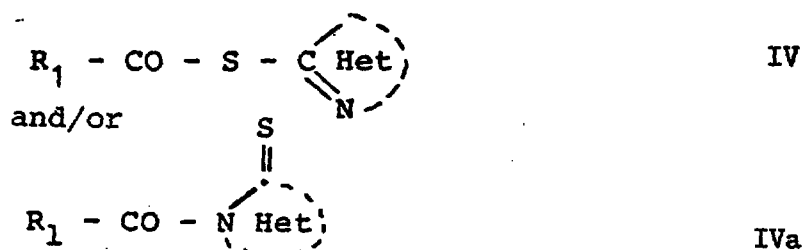


R_2 denotes hydrogen, the acetoxy, the carbamoyloxy, a S-Y- group, whereby Y signifies an unsubstituted or substituted heterocycle, or R_2 denotes an optionally substituted pyridinium of formula



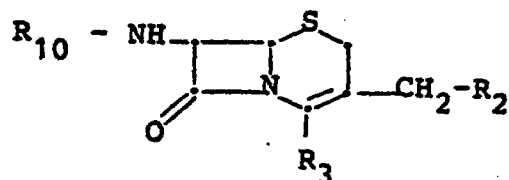
whereby R_8 and R_9 are the same or different and each denotes hydrogen, halogen, alkyl, hydroxy, carboxamido, alkoxycarbonyl, amino, monoalkylamino or dialkylamino, or together signify an optionally substituted, 5- or 6-membered, carbocyclic ring, and R_3 signifies the carboxyl, the carboxylate or a carboxylic acid ester group, characterised by reacting a compound of formula





wherein R_1 is defined as above, and $\text{C} \begin{array}{c} \text{Het} \\ \diagdown \\ \text{N} \end{array}$ resp. $\text{N} \begin{array}{c} \text{S} \\ \parallel \\ \text{Het} \end{array}$

denote a 5- or 6-membered heterocycle, which may contain in addition to the N-atom one or two further heteroatoms, for example O, N and S, and which may be substituted or anellated with an optionally substituted benzene ring, with a compound of formula



V

wherein R_2 and R_3 are defined as above, and R_{10} denotes hydrogen or an amino protecting group, and if desired, deprotecting a final product obtained and optionally converting a final product obtained, in which R_3 denotes COOH , into a salt, or vice versa.

2. Process according to claim 1, wherein in the compounds of

formula IV, $\text{C} \begin{array}{c} \text{Het} \\ \diagdown \\ \text{N} \end{array}$ denotes 2-pyridyl.



3. Process according to claim 1, wherein in the compounds of

formula IV, $\text{-C} \begin{array}{c} \diagup \\ \text{Het} \\ \diagdown \\ \text{N} \end{array}$ denotes 2-benzothiazolyl.



* C L M S *