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Preliminary communication

HETERODISUBSTITUTED FERROCENE DERIVATIVES; β-LACTAMIC ANTIBIOTICS

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Summary

The influence of the ferrocenyl residue on the antimicrobial activity of β-lactamic antibiotics was studied and the reaction conditions fixed for the formation of 1,1′-ferrocenyldicarboxamidopenicillanic (IX) and 1,1′-ferrocenyldicarboxamidocephalosporanic acid (Xa and Xb). The products were characterized as both acids IX and sodium salts X by IR and UV spectra as well as by thin-layer chromatography. The compounds IX and X show antimicrobial activity towards some Gram positive germs.

Most β-lactamic antibiotics used in medical practice are obtained by semisynthesis. The modification of aromatic or heteroaromatic side chains of the penicillins or cephalosporins by substituent introduction affects their activity and the susceptibility to β-lactamase.

The organometallic complexes of the transitional metals introduced in the 6-position of penicillin and in the 7-position of cephalosporin improve the resistance of these antibiotics toward β-lactamase as well as their pharmacological activity [1].

Due to the stability of the ferrocene molecule, its capacity for substitution reactions, the low toxicity, the easy accessibility as well as the possibility of being an iron source for the organism, the ferrocene antibiotics synthesized quite recently [2] are the first semisynthetic antibiotics containing an organometallic residue.

The literature sources for these antibiotics are rather few [2—5], only compounds of structures I—IV being mentioned, in which L stands for either a

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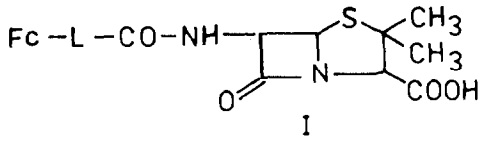
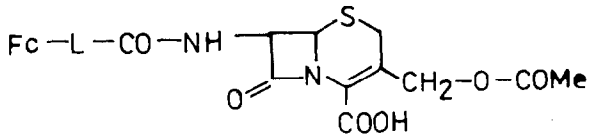


I



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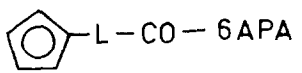

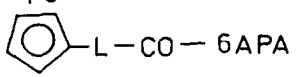

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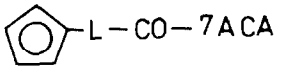
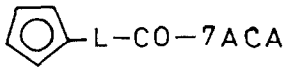




IV

bond (I, II) or a bonding group (I—IV) and Fc denotes the ferrocenyl residue. The 1,1-heterodisubstituted ferrocene led to mixed antibiotics containing penicillanic and cephalosporanic residues with a wide activity spectrum [2,5].

Since the antibiotics containing heterodisubstituted ferrocene were studied less, only the formation of β-lactamic antibiotics with two residues of penicillanic or cephalosporanic acid is reported.

Results and discussion

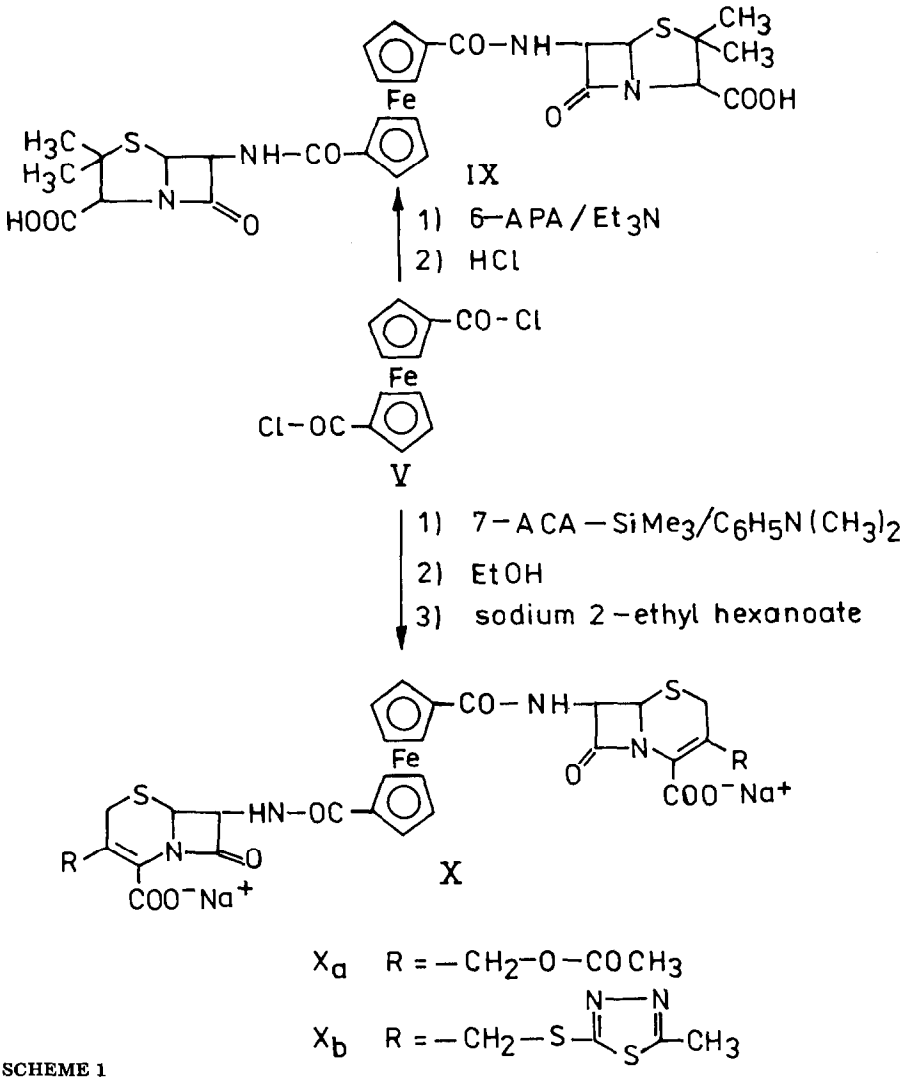
Introduction of the ferrocenyl residue by acylation of 6-aminopenicillanic (VI) or 7-aminocephalosporanic (VII, VIII) acid was performed, either by treatment of ferrocene mono- or di-carboxylic acid chloride with dicyclohexylcarbodiimide [1] or by reaction of ferrocenylendiacetic acid anhydride with trimethylsilylester of 6-aminopenicillanic acid [4].

We used ferrocenylendicarboxylic acid chloride as the acylating agent (V) because the acid was inefficient in the reaction, although the synthesis was rather difficult and the product showed low stability.

The 1,1-bis(chlorocarbonyl)ferrocene (V) was obtained from 1,1′-diacetylferrocene [6—8] "via" ferrocenylen-1,1′-dicarboxylic acid [9].

6-Aminopenicillanic (VI), 7-aminocephalosporanic (VII) and 7-amino-2-(2-methyl-1,3,4-thiadiazol-5-thiomethyl)cephalosporanic (VIII) acids were used as reagents for the 1,1′-bis(chlorocarbonyl)ferrocene, according to reaction scheme 1.

1,1′-Ferrocenylendicarboxamidopenicillanic acid (IX) was obtained by condensation of compound V with the 6-aminopenicillanic acid (VI) in the presence of triethylamine. The penicillin triethylammonium salt was converted into a



SCHEME 1

dark-red acid (IX). The reaction gave a yield of 22%, the resulting penicillin having a purity of 80% as determined chromatographically.

1,1′-Ferrocenylenedicarboxamidocephalosporanic acid (IX) was similarly synthesized by treatment of 1,1′-bis(chlorocarboxyl)ferrocene (V) with the trimethylsilylic ester of compounds VII and VIII, respectively, in the presence of dimethylaniline. Subsequent treatment with sodium 2-ethylhexanoate led to the yellow crystalline disodic salt. The yields were 40% (Xa) and 50% (Xb), respectively, and the purities 98% (Xa) and 88—90% (Xb) as determined chromatographically.

The β-lactamic antibiotics obtained were characterized by elemental analysis, IR and UV spectral measurements, as well as by thin-layer chromatography.

IR spectra were recorded on a UNICAM SP 200 spectrophotometer in KBr pellets. The intense absorption bands found are characteristic for the β-lactamic

$\rangle C{=}O$ group at 1770 cm^{-1} (IX) and 1780 cm^{-1} (Xa, Xb), respectively, and for the secondary amidic $\rangle C{=}O$ group at 1640 and 1520 cm^{-1} (IX), 1640, 1540 cm^{-1} (Xa) and 1650, 1540 cm^{-1} (Xb), respectively. The other bands are due to the ferrocene nucleus (840, 1040, 1100, 1400 cm^{-1}) and to the penicillanic or cephalosporanic residue, respectively.

UV spectra recorded on a UNICAM SP 700 spectrophotometer show λ_{max} at 259 nm (Xa) and 255 nm (Xb).

The elemental analysis data and the spectral measurements confirm the structures proposed for the products IX, Xa and Xb [10].

Biological activity. Due to the structural similarity of penicillins and cephalosporins (both contain a β-lactamic ring, a thiazolidinic or dehydrothiazinic ring with sulphur, a COOH substituent and the same configuration of the chiral centers) similar actions on microorganisms might be assumed, namely blocking of a transpeptidation reaction as a consequence of the acylation implying the β-lactamic ring. The lability of the β-lactamic bond affects the antibiotic activity of these compounds by inactivation of penicillino- or cephalosporino resistant enzymes in the bacterial cell membrane. Modifications in the molecule which increase the stability of the β-lactamic ring result in diminished antimicrobial activity [11].

The minimum inhibitory concentration was tested on a set of nine germs. Compounds IX and X are active towards Bacillus subtilis, Sarcina lutea, Pseudomonas aeruginosa (Xb), Staphylococcus aureus (Xb), and Staphylococcus resistant (Xb) and inactive towards Gram negative germs. Among the compounds studied compound Xb shows a higher antimicrobial activity towards Gram positive germs.

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