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Monosubstituted derivatives of ferrocene. Ferrocene-containing penicillins and cephalosporins *

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Abstract

Six new penicillins and six new cephalosporins have been obtained through acylation (using the mixed-anhydride technique) of 6-aminopenicillanic acid and 7-aminocephalosporanic acid with *S*-(1-ferrocenylalkyl)thioglycolic and *S*-(1-phenyl-1-ferrocenylmethyl)thioglycolic acids. The products were characterized as natrium salts, through spectroscopic analysis (IR, UV) and TLC. Their biological activity towards Gram-positive bacteria is comparable to that of amoxicillin, carbenicillin and cephalothin, while their activity towards Gram-negative bacteria was insignificant.

Introduction

In recent years, penicillins and cephalosporins containing ferrocenyl or 1,1′-ferrocenylene substituents, with a significant biological activity, have been obtained [1,2].

Ferrocene is of special interest in reactions that involve grafting onto penicillinic or cephalosporinic nuclei, because it has two aromatic rings that can undergo substitution. Thus, the antibiotic molecule may be modified into three dimensions, without changing the molecular profile required for biological activity.

In addition, ferrocene (known as an accessible, chemically stable substance, with low toxicity towards mammals) represents a potential source of iron for the organism [3].

Several β-lactamic antibiotics incorporate differently substituted acetyl groups. Also, commercial products frequently contain substituents with sulphur atoms, inserted into a thiophenic, thiadiazolic, thiazolic heterocycle or in a thioetheric bridge.

* Dedicated to Professor O.A. Reutov on the occasion of his 70th birthday on September 5th, 1990.
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This paper discusses the synthesis and properties of some penicillins and cephalosporins containing, in their molecule, mercaptoacetyl radicals that have been S-modified with ferrocene.

Results and discussion

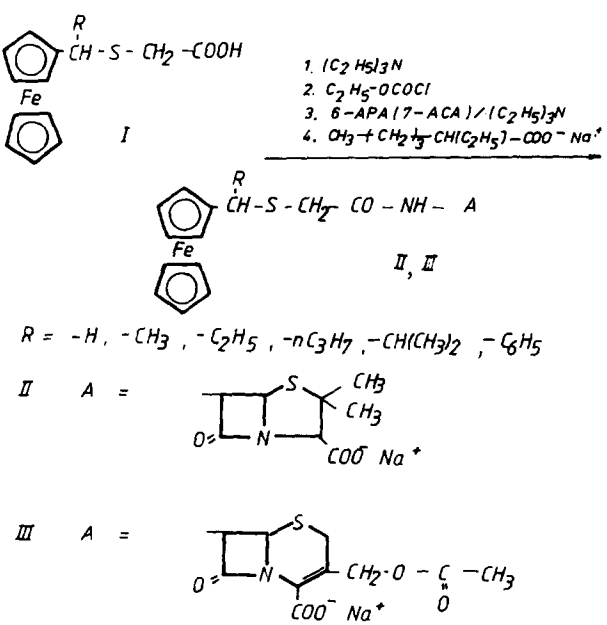
These new β-lactamic ferrocene-containing antibiotics were obtained through acylation of the 6(7)-amino group from 6-aminopenicillanic (6-APA) and 7-aminocephalosporanic (7-ACA) acids with S-modified derivatives of thioglycolic acid (I).

Difficulties encountered in the synthesis of the acid chlorides of derivatives I required the application of the mixed-anhydride technique for acylation (Scheme 1).

Mixed anhydrides were prepared by the reaction of triethylammonium salts of acids I, dissolved in anhydrous CH_2Cl_2, with ethyl chloroformate, in the presence of catalytic amounts of *N*-methylmorpholine. Owing to the instability shown by this type of anhydride, the reaction was performed at temperatures ranging between -25 and $-30\,^{\circ}C$.

The complete transformation of the acid into a mixed anhydride was monitored through TLC (Silicagel FG-254, 10/2 benzene–acetone). The non-transformed acid remained as a triethylammonium salt at the starting point of the chromatographic plate. The mixed anhydride (unstable at room temperature) was detected as its ethyl ester; in all cases, transformation of the acid into a mixed anhydride was complete after 15 min.

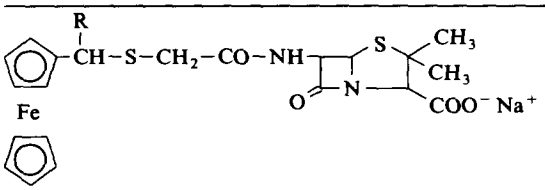
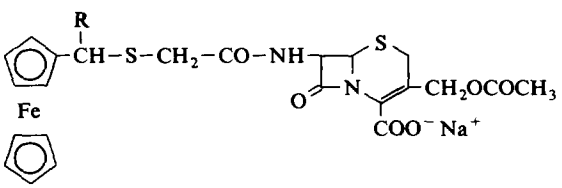
As a rule, acylation was performed by addition of the solution containing the mixed anhydride to a dichloromethanic solution of 6-APA or 7-ACA solubilized as its triethylammonium salt.



Scheme 1

Table 1

Characteristics of the monosubstituted ferrocene-containing penicillins and cephalosporins

No.	R	Yields (%)	IR cm^{-1}				UV λ (nm)
			CO β-Lactamic	CO amidic	$-CH_2OCOCH_3$	$-COO^-$	
							
1	H	40.1	1776	1720	–	1610	–
2	CH_3	47.7	1778	1740	–	1602	–
3	C_2H_5	57.6	1775	1716	–	1604	–
4	C_3H_7	61.5	1776	1712	–	1604	–
5	$CH(CH_3)_2$	60.5	1776	1716	–	1608	–
6	C_6H_5	62.4	1772	1712	–	1602	–
							
7	H	63	1764	1704	1232	1616	258
8	CH_3	60.5	1756	1700	1232	1602	260
9	C_2H_5	48.9	1760	1702	1236	1606	262
10	C_3H_7	52.5	1762	1702	1232	1602	260
11	$CH(CH_3)_2$	55.7	1762	1700	1236	1610	260
12	C_6H_5	45.4	1760	1702	1235	1606	259

As 7-ACA reacted more slowly and in lower yields with mixed anhydrides in comparison with 6-APA, the reaction times were different, i.e. 1 h for the acylation of 6-APA and 1.5 h for 7-ACA. The reaction occurred at -25 to $-30\,^{\circ}C$.

The β-lactamic ferrocene-containing antibiotics were isolated as natrium salts, obtained by treating their acid forms with a solution of sodium 2-ethylhexanoate in isopropanol. Unlike the majority of β-lactamic antibiotics, known to be insoluble in dichloromethane as sodium salts, all the compounds we synthesized were soluble in this solvent; we consider this property to derive from the presence of a ferrocenic nucleus. Consequently, isolation of the sodium salts was made through precipitation in non-solvents (petroleum ether or n-hexane).

The yields ranged between 40.1 and 62.4% for the penicillins and 49.9–60.5% in the case of the cephalosporins (Table 1).

The β-lactamic antibiotics obtained were characterized through IR and UV spectroscopy and TLC. The IR spectra show bands caracteristics of the β-lactamic =CO and amidic =CO and $-COO^-$ groups (Table 1). The presence in the UV spectra of the cephalosporins, of a maximum at about 260 nm, confirms, once more, the integrity of the β-lactamic cycle.

The antimicrobial activity of the synthesized compounds was tested towards Gram-positive (*Staphylococcus aureus*, *Baccillus subtilis* and *Sarcina lutea*) and Gram-negative (*Klebsiela pneumonie* and *Pseudomonas aeruginosa*) bacteria, through the measurement of diameters of the inhibition zones, and compared with the activity of amoxicillin, carbenicillin and cephalothin. The synthesized products showed a good activity against Gram-positive bacteria, equal to or higher than the control samples employed; thus, the activity of the natrium salt of 6-(*S*-ferrocenylmethylmercaptoacetamido)penicillanic acid was higher than that of all control samples.

On Gram-negative bacteria, these products showed no activity.

The results obtained showed that antibacterial activity is not influenced by the nature of the radical R, although a slight but insignificant decrease in activity may be observed on increasing the chain length.

Experimental

Instrumentation

The IR measurements were performed using a Carl Zeiss M 80 spectrometer on solutions of the compounds in Nujol, while the UV spectra were obtained in aqueous solution on a VSU 2P spectrometer (Carl Zeiss). The degree of purity of the obtained products was estimated by TLC, on Silicagel FG-254 supplied by Merck.

Starting materials

The acids I were synthesized from their corresponding hydroxylated derivatives by reaction with thioglycolic acid in the presence of trifluoroacetic acid (TFA) [5–7].

General procedures

To a solution containing 4 mmol of acid I and 0.56 ml (4 mmol) triethylamine in 20 ml anhydrous CH_2Cl_2, at a temperature of -25 to $-30\,^{\circ}C$, 0.38 ml (4 mmol) ethyl chloroformate and 2 drops of *N*-methylmorpholine were added. The reaction mixture was stirred at -25 to $-30\,^{\circ}C$ for 15 min. Over the solution of mixed anhydride, a solution containing 4 mmol of 6-APA or 7-ACA and 1.12 ml (8 mmol) triethylamine in 20 ml anhydrous CH_2Cl_2 was added at -25 to $-30\,^{\circ}C$. The reaction mixture was stirred at -25 to $-30\,^{\circ}C$ for 1 h in the case of 6-APA acylation and 1.5 h for the acylation of 7-ACA, and was then brought to a temperature of 0–5 °C before undergoing extraction with 20 ml water acidified with HCl (pH 2). The organic layer was washed with 20 ml cold water, then 0.2 g charcoal and 5 g anhydrous $MgSO_4$ were added, followed by stirring for 10 min and filtration; 2.2 ml of an isopropanolic solution of natrium 2-ethylhexanoate (concentration 30%) was then added. The solution was concentrated at low pressure to 15 ml and precipitated in 30 ml n-hexane (petroleum ether), filtered, washed with 20 ml n-hexane and finally dried in a vacuum desiccator.

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