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Heterodisubstituted derivatives of ferrocene. Ferrocene-containing penicillins and cephalosporins

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Abstract

The paper discusses the synthesis and properties of five new penicillins and five new cephalosporins with ferrocene, obtained through acylation (the mixed-anhydride technique) of 6-aminopenicillanic and 7-aminocephalosporanic acid with 1,1′-bis[1-(carboxymethyl)thioalkyl]ferrocene and 1,1′-bis[1-(carboxymethyl)thio-1-phenylmethyl]ferrocene.

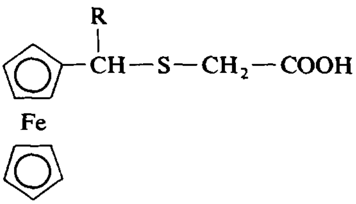
The β-lactamic derivatives obtained have been characterized as natrium salts, through spectroscopic (IR and UV) analyses, as well as through TLC.

These products show good activity against Gram-positive bacteria, comparable to that of amoxicillin, carbenicillin and cephalotin, while their activity towards Gram-negative bacteria was found to be insignificant.

Introduction

A special concern within our investigation aimed at obtaining new β-lactamic antibiotics with ferrocene in their molecules was represented by the synthesis of new 1,1′-symmetrically disubstituted derivatives.

The starting point was provided by the significant results obtained through the acylation of 6-aminopenicillanic (6-APA) and 7-aminocephalosporanic (7-ACA) acids with mercaptoacetic acid derivatives, S-modified with ferrocene-containing radicals, I [1].



(I)

(I, $R = -H, -CH_3, -C_2H_5, -C_3H_7, -CH(CH_3)_2, -C_6H_5$)

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These antibiotics, obtained through acylation with acids of the general structure of I, show remarkable activity against Gram-positive bacteria, comparable to those of some commercial products (amoxicillin, carbenicillin and cephalothin).

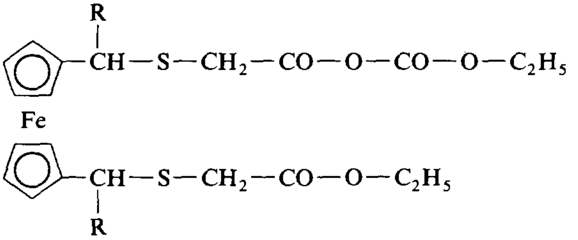
The use of some diacids of type II as acylating agents could be of interest owing to the presence of two β-lactamic nuclei, concomitant with a modification of the molecular profile into three dimensions.

Results and discussion

New penicillins and cephalosporins (containing 1,1′-disubstituted ferrocene in the molecule through the acylation of 6-APA and 7-ACA with derivatives of type II) have been obtained.

The most suitable method to obtain these new β-lactamic antibiotics is the mixed-anhydride technique (Scheme 1).

Mixed anhydrides have been synthesized through the reaction of acids II with ethyl chloroformate, in the presence of triethylamine, using *N*-methylmorpholine as catalyst. The reaction temperature was selected taking the thermal instability of this type of anhydride into consideration. In order to limit the partial decomposition of these mixed anhydrides (a reaction that would lead to structures such as V) the temperature was kept between −40 and −45 °C, unlike acylation with type I acids, whose reaction temperatures ranged between −25 and −30 °C [1].



(V)

The reaction time was 15 min. The transformation of the acid II into a mixed anhidride was monitored by thin-layer chromatography (TLC) (Silicagel FG-254, 10/2 benzene-acetone).

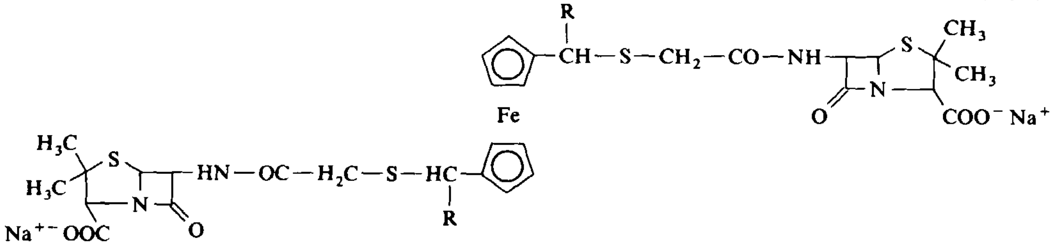
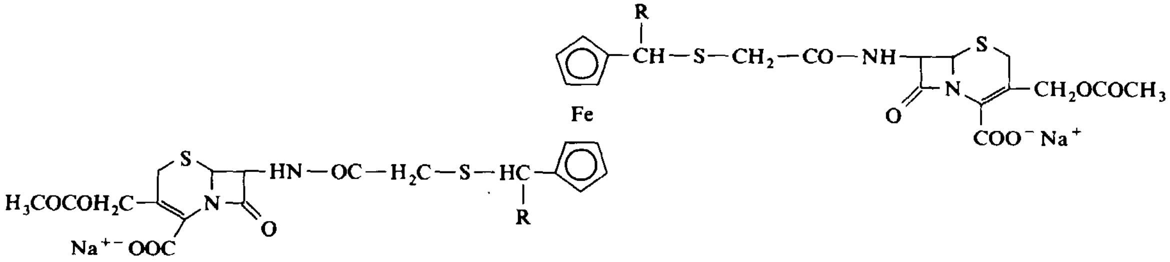
The acylation was conducted at temperatures of −40 to −45 °C, the dissolution of 6-APA and 7-ACA being performed through their transformation into triethylammonium salts; the reaction time for acylation was 1 h for of 6-APA and 1.5 h, for 7-ACA.

The products were isolated as natrium salts, obtained through the treatment of the acid forms with natrium 2-ethylhexanoate. These salts, soluble in CH_2Cl_2, were precipitated with n-hexane or petroleum ether. The β-lactamic derivatives III and IV were obtained at yields ranging between 51.8 and 63.5% (Table 1).

Characterization of the synthesized products was made spectroscopically (IR and UV) and through TLC analyses. The IR spectra show bands characteristic of the $>$CO β-lactamic, $>$CO amidic and COO^- groups (Table 1). The UV spectra of the cephalosporins exhibit a maximum at about 260 nm, attesting, once more, to the integrity of the β-lactamic cycle [2,3].

Their antibacterial activity was tested on Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis* and *Sarcina lutea*) and Gram-negative ones (*Klebsiela*

Table 1. Characteristics of the heterodi-substituted ferrocene-containing penicillins and cephalosporins

No.	R	Yield (%)	IR, cm^{-1}				UV
			CO(β-lactamic)	CO(amidic)	$-CH_2OCOCH_3$	COO^-	λ, nm
							
1	$-CH_3$	55,6	1772	1714	-	1606	-
2	$-C_2H_5$	58,6	1774	1718	-	1602	-
3	$-C_3H_7$	55,2	1774	1716	-	1602	-
4	$-CH(CH_3)_2$	52,7	1772	1726	-	1616	-
5	$-C_6H_5$	51,8	1776	1715	-	1605	-
							
6	$-CH_3$	63,5	1760	1704	1234	1604	260
7	$-C_2H_5$	60,7	1760	1702	1232	1606	262
8	$-C_3H_7$	62,5	1762	1702	1230	1602	262
9	$-CH(CH_3)_2$	55,6	1762	1606	1230	1606	260
10	$-C_6H_5$	52,3	1760	1704	1234	1602	258

pneumonie and *Pseudomonas aeruginosa*), and also compared with the activity of amoxicillin, carbenicillin and cephalothin by measuring the diameters of the inhibition zones.

The activity of these new ferrocene-containing antibiotics towards Gram-positive bacteria is similar, or slightly lower than, that of the control samples employed. The activity towards Gram-negative bacteria was found to be insignificant.

The biological activity of the heteroannular symmetrically disubstituted antibiotics III and IV is comparable to or lower than that of the monosubstituted derivatives obtained through acylation with type I acids [1]. The fact that 1,1′-disubstituted derivatives do not show a significantly higher activity than that of the monosubstituted species may be explained in terms of the much more complex structure of the molecule, which diminishes access to the reactive zones of the enzymes involved in the biosynthesis of the bacterium's cell wall.

Experimental

Instrumentation

The IR measurements were performed using a Carl Zeiss M 80 spectrometer on solutions of the componds in Nujol, while the UV spectra were obtained in aqueous solution on a VSU 2P spectrometer (Carl Zeiss).

Starting materials

The acids II were synthesized from corresponding dihydroxylated derivatives through the reaction of thioglycolic acid, in the presence of trifluoroacetic acid [4].

General procedures

To a solution containing 2 mmol of acid II and 0.56 ml (4 mmol) triethylamine in 20 ml anhydrous CH_2Cl_2, brought to -40 to $-45\,^\circ C$, 0.38 ml (4 mmol) ethyl chloroformate and 2 drops of *N*-methylmorpholine were added. The reaction mixture mixture was stirred at -40 to $-45\,^\circ C$ for 15 min; the transformation of the acids was monitored through TLC.

To a solution of the mixed anhydride, a solution containing 4 mmol of 6-APA or 7-ACA was added, as well as 1.12 ml (8 mmol) triethylamine in 20 ml anhydrous CH_2Cl_2, at -40 to $-45\,^\circ C$. The reaction mixture was stirred at -40 to $-45\,^\circ C$ for 1 h for the acylation of 6-APA and for 1.5 h for the acylation of 7-ACA; its temperature was then increased to 0 to 5 °C and extraction with 20 ml water acidified with HCl (pH 2) was carried out. The organic layer was washed with 20 ml cold water, 0.2 g coal and 5 g $MgSO_4$ were added, stirred for 10 min and filtered; 2.2 ml of an isopropanolic solution of 30% sodium 2-ethylhexanoate was then added. The solution obtained was concentrated at low pressure to 15 ml and precipitated in 30 ml n-hexane (petroleum ether); the precipitate was filtered, washed with 20 ml n-hexane and dried in a vacuum desiccator.

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1 Unpublished results from this laboratory.

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