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MONO- AND HETERODI-SUBSTITUTED DERIVATIVES OF FERROCENE; β-LACTAMIC ANTIBIOTICS *

CR. SIMIONESCU, TATIANA LIXANDRU, D. SCUTARU and M. VÂŢĂ

Department of Organic Chemistry, Polytechnic Institute of Jassy, Str. 23 August, Nr 11, 6600 Jassy (Romania)

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Summary

The ferrocenylsulphonamidopenicillanic (I), -cephalosporanic (II) and -deacetoxycephalosporanic (III) acids and 1,1′-ferrocenylendisulphonamidopenicillanic (IV), -cephalosporanic (V) and -deacetoxycephalosporanic (VI) acids were synthesized and the optimum conditions determined. The products obtained were characterized as their sodium salts by thin-layer chromatography and IR spectral measurements. Compounds II, IV, V and VI show activity towards Gram-positive germs.

Modification of the aromatic or heteroaromatic chain of β-lactamic antibiotics affects both the biochemical action and susceptibility to β-lactamase.

Organometallic compounds of the transition metals used as the acylating agents of 6-aminopenicillanic and 7-aminocephalosporanic acids improve the resistance of the corresponding antibiotics to β-lactamase as well as their pharmacological activity [1].

Ferrocene derivatives were the first compounds used to obtain semisynthetic β-lactamic antibiotics [2], ferrocene being an accessible compound of low toxicity and a possible iron source for the organism.

The rather few references on antibiotics containing the ferrocene residue indicate the chlorides and anhydrides of mono- and dicarboxylic acids act as the acylating agents of 7-aminopenicillanic and 7-aminocephalosporanic acids [2–6].

β-Lactamic antibiotics with a sulphonamide group adjacent to the β-lactamic ring have been rather less studied [7,8]. In the present paper, we report the synthesis of this type of penicilline and cephalosporine by the acylation of 6-aminopenicillanic and 7-aminocephalosporanic acids with ferrocenyl sulphochloride and 1,1′-ferrocenylendisulphochloride.

* Dedicated to Professor O.A. Reutov on the occasion of his 65th birthday on 5 September 1985.

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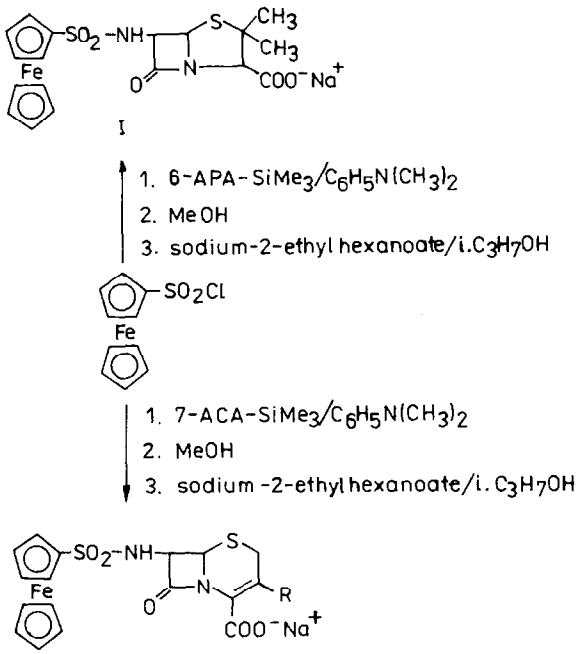
Results and discussion

The ferrocene mono- and di-sulphochlorides were synthesized from the corresponding sulphonic acids according to literature methods [9,10] modified by us. The sulphonic acid was converted to the *p*-toluidine salt and then treated with PCl_3. The sulphochlorides had previously been purified chromatographically. They were subjected to condensation with 6-aminopenicillanic (6-APA), 7-aminocephalosporanic (7-ACA) and 7-aminodeacetoxycephalosporanic (7-ADCA) acids as trimethylsilyl esters (Schemes 1 and 2).

SCHEME 1



I

II R = $-CH_2-O-CO-CH_3$

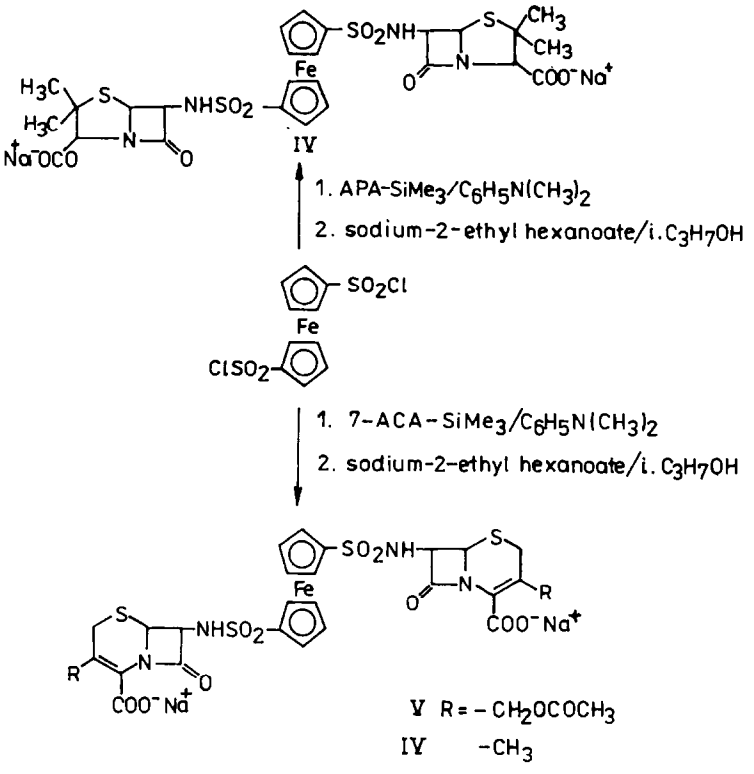
III R = $-CH_3$

TABLE 1

CHARACTERISTICS OF COMPOUNDS I–VI

Product	Characteristic IR bands, frequency (cm^{-1})					Reaction yield (%)
	CO β-lactamic	SO_2 *sym*	SO_2 *asym*	NH	COO^-	
I	1760	1200	1340	3400	1610	58.8
II	1740	1140	1340	3170	1610	70
III	1760	1155	1350	3400	1610	89
IV	1760	1150	1380	3400	1610	65.5
V	1780	1140	1340	3200	1620	71
VI	1780	1150	1350	3400	1620	32.7

SCHEME 2



The condensation was carried out by refluxing the reaction mixture containing dimethylaniline and ethyl acetate as solvent. Treatment with sodium 2-ethylhexanoate yielded the corresponding sodium salts, light yellow to brown in colour. Products of about 90% purity (estimated chromatographically), in yields ranging from 32.7 to 89% (Table 1), were thus obtained.

The compounds synthesized, I–VI, were characterized by means of thin-layer chromatography as well as by IR spectral measurements.

The IR spectra were recorded on a UNICAM SP 200 spectrophotometer in KBr pellet. In all the spectra, bands characteristic of the β-lactamic $>C=O$ group (1740–1780 cm^{-1}), SO_2 *sym* (1140–1200 cm^{-1}) and SO_2 *asym* (1340–1380 cm^{-1}), $>NH$ (3170–3400 cm^{-1}), and COO^- (1610, 1620 cm^{-1}), as well as absorptions of the ferrocene ring and penicillanic and cephalosporanic residues (Table 1) were observed.

The biological activity of compounds I–VI was tested by determining the diameter of the inhibition region and the minimum inhibiting concentration. Compounds I, IV, V and VI are active towards *Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli* and inactive towards Gram-negative germs.

Among the compounds synthesized, 1,1′-ferrocenylendisulphonamidopenicillanic acid (IV) shows the highest antimicrobial activity to Gram-positive germs.

The biological activity of ferrocene-sulphonamido- and -disulphonamido-penicil-

lanic (cephalosporanic) acids is lower than that of the corresponding carboxamido acids [6].

The biological activity data obtained by us are in agreement with the literature data indicating a lower activity for the sulphonamido-β-lactamic antibiotics in comparison with the carboxamidones [7,8,11]. The sulphonamido group probably increases the stability of the β-lactamic ring, thus decreasing the antimicrobial activity [12].

Experimental

Ferrocenylsulphoamidopenicillanic (I), -cephalosporanic (II) and -deacetoxycephalosporanic (III) acids

1.5 mol/mol of 6-APA (7-ACA) hexamethyldisilazane was added to a suspension of 6-APA (or 7-ACA) (0.001 mol) in 10 ml of anhydrous ethyl acetate and refluxed for 1.5–2 h until dissolution. The solution was then cooled to 10–15°C, dimethylaniline (1 mol/mol 6-APA or 7-ACA) and a solution of ferrocenylmonosulphochloride in 10 ml of ethyl acetate were added, and the mixture was refluxed for 2 h under stirring. The reaction mixture was filtered and the solution was treated with 0.3 ml of methanol (5 mol/mol 6-APA) and again filtered. To the filtrate was added 0.75 ml of an isopropanolic solution of sodium 2-ethylhexanoate (26.4%) and the mixture was allowed to stand for 30 min at room temperature. The sodium salt was filtered, washed with ethyl acetate, and dried under vacuum.

1,1'-Ferrocenylendisulphonamido-penicillanic (IV), cephalosporanic (V) and -deacetoxycephalosporanic (VI) acids

To a suspension of 6-APA or 7-ACA (0.001 mol) in 10 ml of anhydrous ethyl acetate, 1.5 mol/mol 6-APA (7-ACA) hexamethyldisilazane was added and refluxed for 1–1.5 h until dissolution. The solution is cooled to 10–15°C and dimethylaniline (1 mol/mol 6-APA or 7-ACA) and a solution of 1,1'-ferrocenylendisulphochloride (0.007 mol) in 20 ml of ethyl acetate were added. The mixture was reflexed for 2 h under stirring. The filtered solution was treated with 1.16 ml of an isopropanolic solution of sodium 2-methylhexanoate (26.4%). The filtrate was reduced to half its volume under vacuum, a four-fold volume of petroleum ether was added and the mixture was allowed to stand at room temperature for 1 h until crystallization was completed. The disodium salt was filtered, washed with petroleum ether, and dried under vacuum.

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