Journal of Organometallic Chemistry, 85 (1975) C23—C25

Preliminary communication

ORGANOMETALLIC DERIVATIVES OF PENICILLINS AND CEPHALOSPORINS A NEW CLASS OF SEMI-SYNTHETIC ANTIBIOTICS

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(Received November 25th, 1974)

Summary

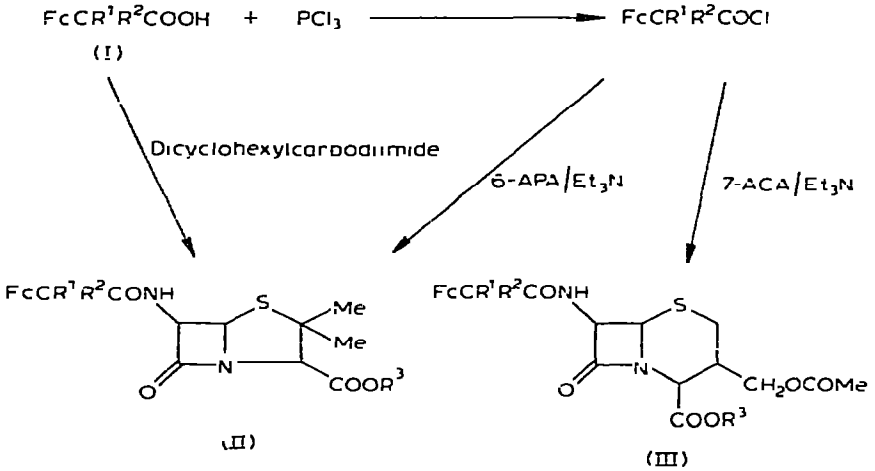
Novel semi-synthetic derivatives of penicillin and cephalosporin have been prepared in which the conventional phenyl or heteroaromatic group has been replaced by a ferrocene moiety, and in which the metal atom is in close proximity to the β-lactam ring of the antibiotic; several of the compounds exhibit high antibiotic activity and others are potent β-lactamase inhibitors.

Currently, there is much interest in the technological uses of the metallocenes [1]. Ferrocene is ideal for use in drug design because of the low toxicity [2] and the ease of substitution of this molecule. In this report we describe the preparation of a number of semi-synthetic penicillins and cephalosporins derived from ferrocene.

Most commercially available semi-synthetic penicillins and cephalosporins possess a side chain that incorporates a phenyl or heteroaromatic group. The introduction of substituents into these nuclei modifies their two dimensional profile and effects changes in the antibiotic activity and β-lactamase susceptibility. The use of ferrocene as the aromatic nucleus in these antibiotics provides, via the second cyclopentadienyl ring, for gross modification in the third dimension of the molecule and also for the introduction of a metal atom in close proximity to the β-lactam ring. The ferrocenylacetic acids (Ia, Ib and Ic) were prepared and treated with phosphorus(III) chloride [3] to give ferrocenylacetyl, 2-ferrocenylpropanoyl and 2-ferrocenyl-2-methylpropanoyl chloride, respectively. These acid chlorides were condensed with 6-aminopenicillanic and 7-aminocephalosporanic acids in the presence of triethylamine to give the ferrocenylpenicillins (IIa, IIb and IIc; R^3 = H) and the ferrocenylcephalosporins (IIIa, IIIb and IIIc; R^3 = H), respectively, in good yields, Scheme 1. Ferrocenylacetic acid was condensed directly with 6-aminopenicillanic acid in the presence of dicyclohexylcarbodiimide [4] to give the ferrocenylpenicil-

lin (IIa; R^3 = H), Scheme 1, which was identical with the compound prepared by the acid chloride route.

scheme 1



Fc = $C_{10}H_9Fe$ 6-APA = 6-aminopenicillanic acid 7-ACA = 7-aminocephalosporanic acid.
a : $R^1 = R^2 = H$; b. $R^1 = H$, $R^2 = Me$, c. $R^1 = R^2 = Me$

The ferrocenylpenicillins were isolated as the sodium salts (IIa, IIb and IIc; R^3 = Na) and their infrared spectra exhibited strong absorptions characteristic of β-lactam ring and secondary amide carbonyl groups (Table 1).

TABLE 1

CARBONYL ABSORPTION FREQUENCIES (cm^{-1}) FOR SOME FERROCENYL-PENICILLINS AND -CEPHALOSPORINS

		β-Lactam carbonyl	Secondary amide carbonyl	Ester carbonyl
IIa	R^3 = Na	1760	1675	—
IIb	R^3 = Na	1750	1660	—
IIc	R^3 = Na	1755	1670	—
IIIa	R^3 = Na	1750	1655	1735
IIIb	R^3 = Na	1750	1655	1730
IIIc	R^3 = Na	1755	1665	1735

The ferrocenylcephalosporins (IIIa, IIIb and IIIc; R^1 = Na) showed similar absorptions together with an absorption characteristic of an ester carbonyl group (Table 1) [5]. The PMR spectra of all these molecules were consistent with the proposed structures [5]. All the ferrocenyl-penicillins and -cephalosporins prepared were shown to be pure by thin layer chromatography. The benzylamine salts (IIa, IIb and IIc; R^3 = $PhCH_2NH_3$) were prepared and characterised but the corresponding ferrocenylcephalosporins (IIIa, IIIb and IIIc; R^3 = $PhCH_2NH_3$) could not be isolated.

In an attempt to overcome this difficulty in the characterisation of labile organometallic derivatives of cephalosporin and penicillin the adamantanamine salts (IIIa, IIIb and IIIc; R^3 = $C_{10}H_{15}NH_3$) were prepared. These

salts were highly crystalline and stable in the atmosphere and were found to be most useful when the usual amine salts could not be isolated.

The ferrocene derivatives (IIa, IIb, and IIc; R^3 = Na) and (IIIa, IIIb and IIIc; R^3 = Na) exhibited antibiotic activity against various strains of *Staphylococcus aureus*. For example the ferrocenylpenicillin (IIa; R^3 = Na) exhibited high antibiotic activity comparable to that of benzylpenicillin. The antibiotic activity decreased with increasing substitution of the α-ferrocenyl carbon atom. The ferrocene derivatives (IIa, IIb and IIc; R^3 = Na) and (IIIa, IIIb and IIIc; R^3 = Na) also behaved as β-lactamase inhibitors. As the degree of substitution of the α-ferrocenyl carbon atom increased their efficiency as inhibitors increased, the α-dimethyl compound (IIa, R^3 = Na) being the best inhibitor. All new compounds exhibited the requisite analytical and spectral properties.

References

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