SEMISYNTHETIC β-LACTAM ANTIBIOTICS.VII. NEW SEMISYNTHETIC CEPHALOSPORINS DERIVED FROM α-SULFOPHENYLACETIC ACID

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The preparation of derivatives of α-sulfophenylacetic acid has been made from 7-aminocephalosporanic acid. New semisynthetic cephalosporins exhibit a peculiar inhibitory effect against Pseudomonas aeruginosa.

Previous reports[1,2,3] from our Laboratory have disclosed the synthesis and structure activity relationships of new semisynthetic penicillins e.g. α-sulfobenzylpenicillin (I). In the course of our studies of this series we became interested in semisynthetic cephalosporins derived from α-sulfophenylacetic acid. Although the attempt to develop new cephalosporins through chemical modification has been done for several years,[4] these derivatives are essentially devoid of anti-pseudomonal activity.

It was expected that α-sulfobenzyl side chain of 7-aminocephalosporanic acid, consisting of highly polar hetero atoms, might exhibit the different antibacterial activity due to its polarities or spatial size of the function.[1] The acylation of 7-aminocephalosporanic acid (III) with the acid chloride II has been attempted in the usual manner, and we have examined displacement reaction of 3-acetoxy group by pyridine nucleophile e.g. pyridine and isonicotinamide. The synthetic route is summarized in Figure 1.

α-Sulfophenylacetic acid chloride (II) was easily obtained in our Laboratory. Sodium 7-(α-sulfophenylacetamide)cephalosporanate (IV) was prepared by the acylation of 7-ACA (III) with Et_2O solution of acid chloride II in an aqueous solution containing $NaHCO_3$ at 0-5°C and the aqueous layer was separated and purified by chromatography on a column of Amberite XAD-2 using water as eluant. The eluate was lyophilized to yield the compound IV.

The displacement reaction of 3-acetoxy group of IV with pyridine nucleophiles was carried out in an aqueous solution saturated with inorganic salts (e.g. potassium thiocyanate, potassium iodide, etc.). Isolation of the product was facilitated by column-chromatography using Amberite XAD-2. The eluate was lyophilized to give the betaine compound. For separation of diastereoisomers of Va and Vb, the fractional crystallization from ethanol-H_2O or acetone-H_2O was recommended. The nmr spectral data are listed in Table 1. The result of <u>in vitro</u> comparison with these cephalosporin derivatives and appropriate penicillin I are listed in Table 2. It is remarkable that D-isomer of betaine derivatives

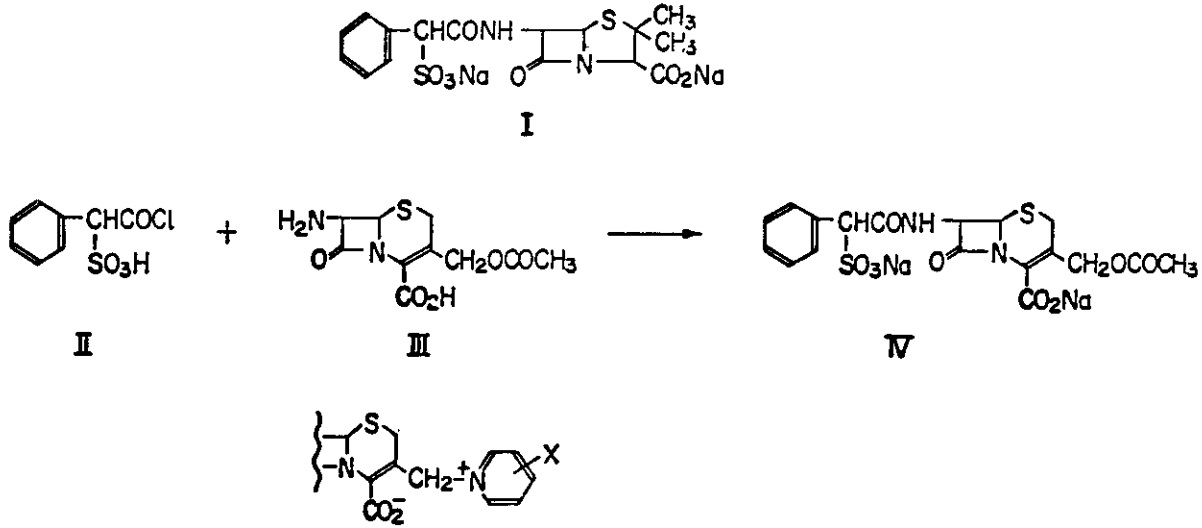
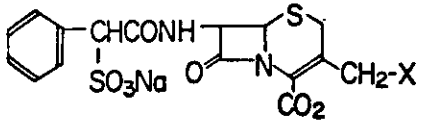

CHCONH
SO3Na
O
S
CH3
CH3
N
CO2Na
I
CHCOCl
SO3H
+
H2N
O
N
S
CH2OCOCH3
CO2H
II
III
CHCONH
SO3Na
O
N
S
CH2OCOCH3
CO2Na
IV
CH2
+
N
X
CO2-
Va, X=H
Vb, X=-CONH2(4')

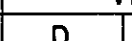
Figure 1

Table I. NMR Spectral Data (D_2O Solution, 60 Mc)

Compound	Chemical shifts, δ -values (J, cps)						
	2-H_2	3-H_2	6-H	7-H	-OCOC$\underline{H}_3$	pH-C$\underline{H}$	Pyridinium
D-IV	3.26(18), 3.56(18)	4.79, 4.82	5.08(4.5)	5.72(4.5)	2.10	5.10 7.51	....
L-IV	3.44(18), 3.84(18)	4.80, 4.86	5.12(5.0)	5.68(5.0)	2.13	5.11 7.50	....
D-Va	2.97(18), 3.35(18)	5.27, 5.40	5.07(5.2)	5.71(5.2)	..	5.10 7.47	8.04, 8.55, 8.90
L-Va	3.21(18), 3.51(18)	5.38, 5.47	5.20(4.8)	5.72(4.8)	..	5.14 7.47	8.09, 8.54, 8.91
D-Vb	2.99(18), 3.56(18)	5.40, 5.51	5.13(4.8)	5.73(4.8)	..	5.10 7.40	8.31(6.6), 9.07(6.6)
L-Vb	3.15(18), 3.68(18)	5.45, 5.56	5.22(4.8)	5.74(4.8)	..	5.08 7.47	8.32(6.5), 9.11(6.5)

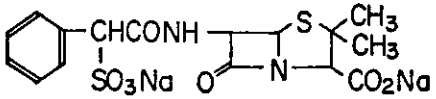
Table.2 Antibacterial Activities of D-and L-Cephalosporins



Organisms	X=	IV		Va		Vb		I	SB-Pc[c]
		D	L	D	L	D	L	D	
		−OAc	−OAc						
Pseudomonas aeruginosa IFO 3080		100	>100	1.56	25	1.56	25	12.5	
P. aeruginosa NCTC 10490		3.12	100	0.39	12.5	0.39	25	3.12	
Staphylococcus aureus 209P		3.12[a]	50	1.56	3.12	3.12	12.5	0.39	
Staph. aureus No. 87[b]		12.5	100	3.12	12.5	3.12	25	6.25	

a. Minimal inhibitory concetration (MIC) in μg/ml as determined by the ager dilution method.

b. Penicillin G-resistant strain.

c. 

V (Va, Vb) exhibits the stronger anti-pseudomonal activity as compared with L-isomer and penicillin I. Structure activity relationships of these new cephalosporins will be reported separately.

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