

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

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The preparation of derivatives of α -sulfophenyl-
acetic 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 semi-
synthetic 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 Et₂O solution of acid chloride II in an aqueous solution containing NaHCO₃ at 0-5°C and the aqueous layer was separated and purified by chromatography on a column of Amberlite 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 Amberlite XAD-2. The eluate was lyophilized to give the betaine compound. For separation of diastereoisomers of Va and Vb, the fractional crystallization from ethanol-H₂O or acetone-H₂O was recommended. The nmr spectral data are listed in Table 1. The result of in vitro comparison with these cephalosporin derivatives and appropriate penicillin I are listed in Table 2. It is remarkable that D-isomer of betaine derivatives

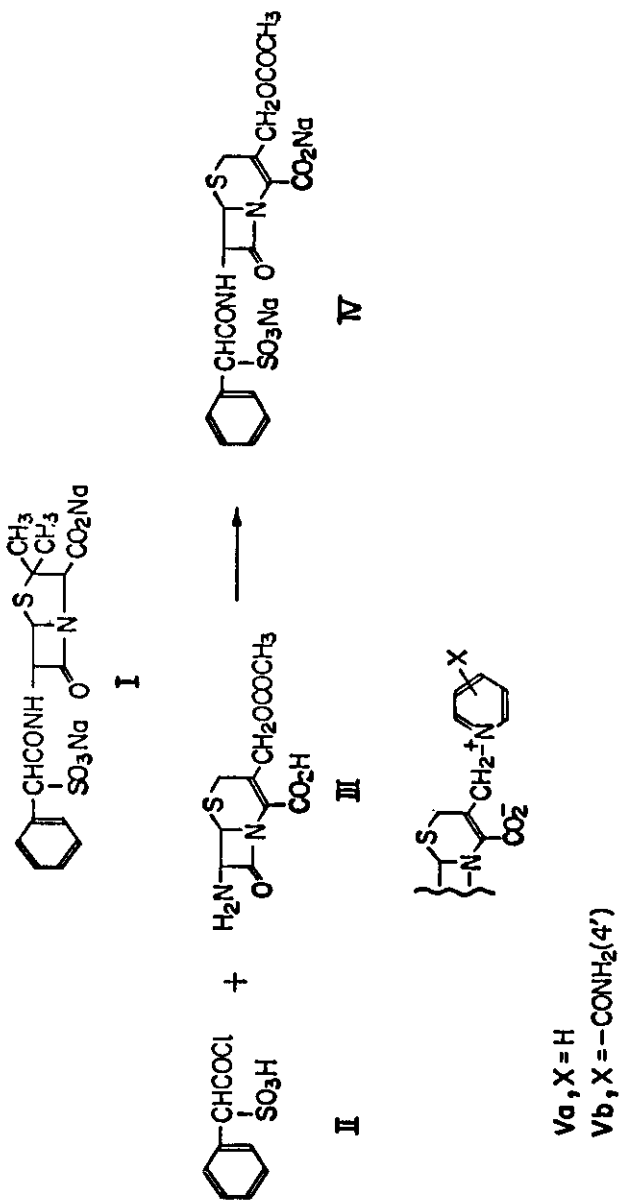
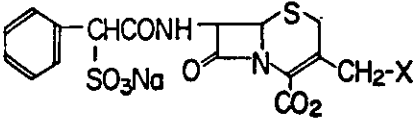


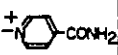
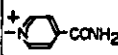


Figure 1

Table I. NMR Spectral Data (D₂O Solution, 60 Mc)

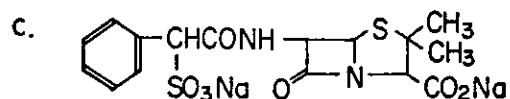
Compound	Chemical shifts, ^a -values (J, cps)							
	2-H ₂	3-H ₂	6-H	7-H	-OCOCH ₃	pH-CH	Pyridinium	
D-IV	3.26(18), 3.56(18)	4.79, 4.82	5.08(4.5)	5.72(4.5)	2.10	5.10	7.51
L-IV	3.44(18), 3.84(18)	4.80, 4.86	5.12(5.0)	5.68(5.0)	2.13	5.11	7.50
D-Va	2.97(18), 3.35(18)	5.27, 5.40	5.07(5.2)	5.71(5.2)	..	5.10	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

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

a. Minimal inhibitory concentration (MIC) in $\mu\text{g/ml}$ as determined by the agar dilution method.

b. Penicillin G-resistant strain.



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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