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ELECTROCHEMICAL REDUCTION OF CEPHALOSPORANIC ACIDS. A NEW SYNTHESIS OF 7-(D-2-AMINO-2-PHENYLACETAMIDO)-3-DESACETOXYCEPHALOSPORANIC ACID

Michihiko Ochiai, Osami Aki, Akira Morimoto, Taiiti Okada,
Kazuo Shinozaki and Yutaka Asahi
Central Research Division, Takeda Chemical Industries, Ltd.,
Juso, Osaka, Japan

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Principally two methods have been available for the synthesis of 7-(D-2-amino-2-phenylacetamido)-3-desacetoxycephalosporanic acid, cephalexin (CEX), which is an orally active cephalosporin antibiotic. The one involves catalytic hydrogenolysis[1,2] of the corresponding cephalosporanic acid and the other a multi-step synthesis *via* the ring expansion of penicillin derivatives.[3]

In this communication will be described a facile electrochemical synthesis of a novel class of cephalosporins, 3-methylenecepham derivatives (II), and a convenient synthesis of CEX *via* these 3-methylenecepham derivatives.

A buffer solution (0.1 M Na_2HPO_4-HCl, pH 6.9, 400 ml) of 7-aminocephalosporanic acid (Ia, 2.0 g) and $NaHCO_3$ (610 mg) was electrolyzed in a cell made from a 1-liter three-necked flask which contained a mercury pool cathode and a horizontal platinum sheet anode, separated from one another by means of a sintered glass partition of medium porosity, at room temperature under stirring at 15 volt for 34 hr until the ultraviolet absorption at 258 nm disappeared. Chromatographic purification on a charcol column gave 7-amino-3-methylenecepham-4-carboxylic acid (IIa, 1.03 g, 64%), mp. 212-214°C (dec), C, 43.76; H, 4.73; N, 12.40; S, 14.43%, $C_8H_{10}N_2O_3S\cdot\frac{1}{4}H_2O$ requires C, 43.92; H, 4.83; N, 12.82; S, 14.65%, IR (KBr); 1770 cm^{-1} (β-lactam), NMR (δ, 100 Mc, CF_3COOD); 3.61 (AB quartet, 2H, 2-C$\underline{H}_2$), 5.18 (doublet, 1H, 6-C$\underline{H}$), 5.36

singlet. 1H, 4-C$\underline{H}$), 5.48 (broad singlet, 2H, 3=C$\underline{H}_2$), and 5.68 (doublet, 1H, 7-C$\underline{H}$).

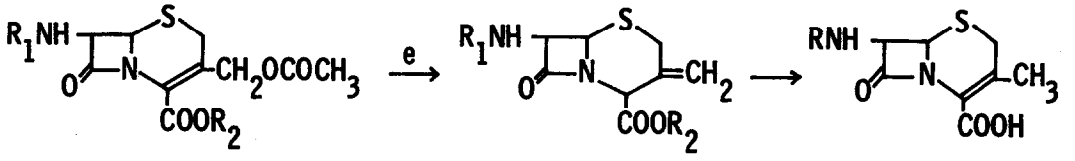
Similarly cephalosporin C (Ib) gave the corresponding 3-methylenecepham derivative (IIb) in 81% yield (15 volt, 5.5 hr). IIb: mp. 205-208°C (dec), C, 40.31; H, 5.65; N, 10.37%, $C_{14}H_{18}O_6N_3SNa\cdot 2H_2O$ requires C, 40.48; H, 5.34; N, 10.12%, IR (KBr); 1760 (β-lactam) and 920 cm^{-1} (=CH_2), NMR (δ, 100 Mc, D_2O); 1.80-3.40 (multiplet, 4H, -C$\underline{H}_2$C$\underline{H}_2$-), 2.61 (triplet, 2H, -C$\underline{H}_2$CO), 3.69 (quartet, 2H, 2-C$\underline{H}_2$), 3.93 (triplet, 1H, N-C$\underline{H}$), 5.15 (singlet, 1H, 4-C$\underline{H}$), 5.44 (doublet, 1H, 7-C$\underline{H}$), and 5.59 (singlet, 2H, =C$\underline{H}_2$).

When a mixture of IIa (32.1 mg) and trimethylchlorosilane (100 mg) in d_5-pyridine (0.4 ml) was stirred overnight at room temperature, IIa was isomerized to 3-desacetoxycephalosporanic acid derivative (IIIa) quantitatively as evidenced by the nmr spectrum.

Amino group of IIa was treated with phenylglycyl chlorides to give the corresponding 3-methylenecepham derivatives (IIc and IId). IIc: mp. 174-178°C (dec), C, 51.73; H, 4.75; N, 10.78%, $C_{16}H_{16}O_4N_3SNa\cdot\frac{1}{4}H_2O$ requires C, 51.40; H, 4.45; N, 11.24%, IR (KBr); 1750 (β-lactam) and 917 cm^{-1} (=CH_2), NMR (δ, 100 Mc, D_2O); 3.50 (quartet, 2H, 2-C$\underline{H}_2$), 5.07 (singlet, 1H, 4-C$\underline{H}$), 5.27 (singlet, 1H, PhC$\underline{H}$), 5.33 (broad singlet, 2H, =CH_2), 5.49 (doublet, 1H, 6-C$\underline{H}$), 5.65 (doublet, 1H, 7-C$\underline{H}$), and 7.68 (broad singlet, 5H, phenyl). IId: mp. 179-181°C (dec), C, 44.41; H, 4.03; N, 7.65%, $C_{20}H_{22}O_8N_3S_2Na\cdot H_2O$ requires C, 44.68; H, 4.50; N, 7.81%, IR (KBr); 1740 cm^{-1} (β-lactam), NMR (δ, 100 Mc, D_2O); 3.32 (singlet, 3H, C$\underline{H}_3$), 3.56 (AB quartet, 2H, 2-C$\underline{H}_2$), 3.77 and 4.72 (two triplets, 4H, -COOC$\underline{H}_2$C$\underline{H}_2$SO_2-), 5.11 (singlet, 1H, 4-C$\underline{H}$), 5.38 (singlet, 2H, =C$\underline{H}_2$), 5.47 (singlet, 1H, NHC$\underline{H}$CO), 5.54 (doublet, 1H, 6-C$\underline{H}$), 5.64 (doublet, 1H, 7-C$\underline{H}$), and 7.61 (singlet, 5H, phenyl).

IIc was isomerized quantitatively as was observed with IIa to the corresponding 3-desacetoxycephalosporanic acid derivative (IIIb), CEX, on treatment with pyridine and trimethylchlorosilane. Thus, a novel and convenient synthetic route for CEX (IIIb) was established. Introduction of phenylglycyl group to IIIa[1] obtained from IIa also afforded CEX.

One-pot synthesis of CEX from IIa can be achieved more conveniently.



I II III

	R_1	R_2	R
I, IIa:	H	H	IIIa: H
b:	$HOOC-CH(CH_2)_3CO$ NH_2	Na	b: C_6H_5-CHCO NH_2 (CEX)
c:	C_6H_5-CHCO NH_2	Na	
d:	C_6H_5-CHCO $NHCOOCH_2CH_2SO_2CH_3$	Na	

Thus IIa (214 mg) was acylated with the HCl salt of phenylglycyl chloride (205 mg) in dichloromethane (15 ml) in the presence of triethylamine (202 mg), dimethylaniline (200 mg) and trimethylchlorosilane (250 mg). IIc thus formed was isomerized without isolation to CEX (154 mg) by the addition of dry pyridine.

Full details of the experimentation as well as mechanistic aspects will be reported elsewhere.

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