Penicillin-Cephalosporin Conversion. XII.[1] Electroreductive Dechlorination of 3′-Chlorocephalosporins into 3-Methylenecephams

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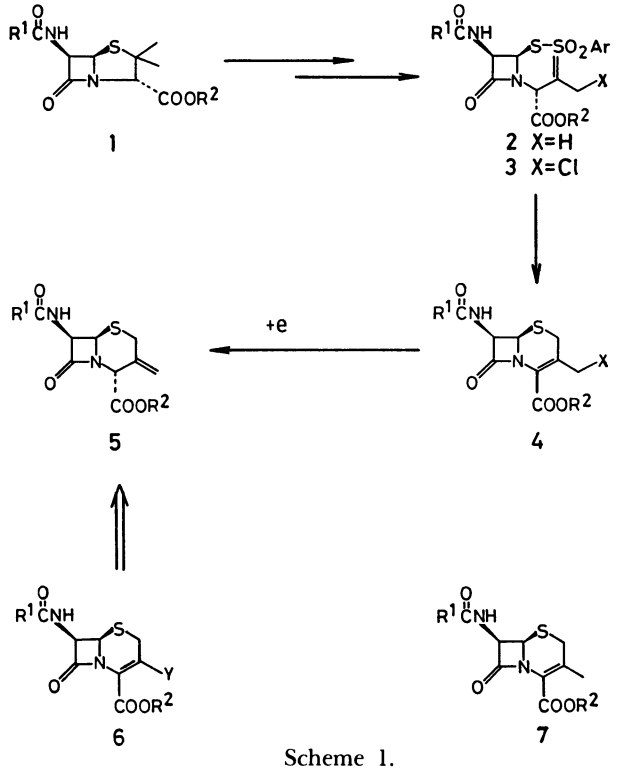
Synopsis. An efficient electroreductive conversion of 3′-chlorocephalosporins and their analogues into the corresponding 3-methylenecephams has been performed in an aqueous THF-$LiClO_4$-(Pb cathode) and/or aqueous MeCN-EtOH-$LiClO_4$-NH_4ClO_4 (Pb cathode) system.

3-Methylenecephams (**5**) are useful precursors of 3-norcephalosporins (**6**), unnatural β-lactam antibiotics, where the C(3)-position directly combines with a heteroatom (Y), e.g., chlorine and methoxy groups.[2] Recently, we have succeeded in exploring a simple and efficient synthetic scheme of 3′-chlorocephalosporins (**4**), which comprises the ene-type chlorination of azetidinone (**2**) derived from natural penicillins and subsequent cyclization of **3** with ammonia (Scheme 1).[3] Consequently, our next efforts were focused on reductive elimination of the chlorine atom at C(3′)- position of **4** as a straightforward access to the 3-methylenecephams. We investigated this possibility by use of electroreductive procedure.



Scheme 1.

Electroreductive elimination of C(3′)-substituents of cephalosporins **4** (X=OAc, SAc, $^+NC_5H_5$, etc.) has been extensively investigated in buffer solution with Hg cathode under controled potential electrolysis conditions.[4] To our knowledge, however, electroreductive conversion of 3′-chlorocephalosporins (**4**) (X=Cl) into the corresponding 3-methylenecephams (**5**) has not been realized. In this paper, we wish to describe an efficient electroreductive elimination of C(3′)-substituents of 3′-chlorocephalosporins (**4**) (X=Cl) and their analogues **4** (X=I and SBT) in a slightly modified electroreductive system, wherein Hg cathode was replaced with Pb cathode and electrolysis was conducted under regulated current density without strict control of the electrode potential.

Electrolysis was carried out in a divided cell fitted with Pt anode and Pb cathode (3 cm^2 each). A mixture of tetrahydrofuran (THF) and H_2O (4/1) containing $LiClO_4$ and NH_4ClO_4 was charged into both compartments of the cell. The cephalosporins **4** (X=Cl, I, SBT, and OAc) were added into the cathode compartment and regulated d.c. power at 3.3 mA cm^{-2} was supplied at room temperature, until most of the starting materials **4** were consumed.

Typical results of electroreductive removal of the C(3′)-substituents of **4** are summarized in Table 1. Electroreduction of 3′-chlorocephalosporins (**4**) (X=Cl) proceeded smoothly and, after passage of 3.5 F mol^{-1} of electricity, afforded the corresponding 3-methylenecephams (**5**), which contained less than 2% of their endo isomers **7** (Entries 1 and 2). Electroreduction of **4a** (R^1, R^2=$PhCH_2$; X=Cl) into **5** was also performed in MeCN-H_2O-EtOH (4/1/0.07) with the same supporting electrolytes (Entry 3), while the electrolysis of **4a** in the absence of ethanol (Entry 4) provided no reduction product. Proper choice of the cathode material is significant. Thus, Pb cathode was indispensable for the successful conversion of **4** into **5**, since the yields of **5** varied depending on the choice of cathode materials in the order: Pb (87%)>C(58%)>Cu (51%)>Pt(19%).

Next, the electroreductive procedure was applied to 3′-iodo-, 3′-(2-benzothiazolylthio)- and 3′-acetoxycephalosporins (**4**) (X=I, SBT, and OAc). Iodide **4c** (X=I) was less effective than chloride **4a** (X=Cl), affording only 64% yield of **5** (Entry 5). It is likely that considerable portion of **4c** would suffer from decomposition in the aqueous electrolysis media prior to the electroreduction. 3′-(2-Benzothiazolylthio)cephalosporin (**4d**) (X=SBT)[5] was smoothly converted to the corresponding 3-methylenecepham (**5**) in 78—90% yields (Entries 6 and 7). On the other hand, 3′-acetoxycephalosporin **4e** (X=OAc) could not be reduced in the present electroreductive media (Entry 8). The almost complete recovery of **4e** was somewhat surprising in comparison with the successful conversion of **4** (X=OAc) to **5** in a buffer solution-(Hg cathode) system, reported by Ochiai, et al.[4a,b] Although scope and limitation of the present electroreductive procedure are still unclear, it is evident that a combination of the electroreductive dechlorination of 3′-chlorocephalosporins **4** (X=Cl)

Table 1. Electroreductive Removal of C(3′)-Substituents of Cephalosporins[a]

Entry	Compound 4[b]	R^1	R^2	X	Solvent	Electricity[c] F/mol	Yield/%[d] 5	7
1	**4a**	$PhCH_2$	PMB	Cl	THF-H_2O(4/1)	3.5	87	—
2	**4b**	$PhCH_2$	$PhCH_2$	Cl	THF-H_2O(4/1)	3.5	84	2
3	**4b**				MeCN-H_2O-EtOH (4/1/0.07)	7	79	—
4	**4b**				MeCN-H_2O(4/1)	7	—	—
5	**4c**	$PhCH_2$	PMB	I	THF-H_2O(4/1)	3.5	64	2
6	**4d**	$PhOCH_2$	$PhCH_2$	SBT	THF-H_2O(4/1)	4.5	78	2
7	**4d**				MeCN-H_2O-EtOH (4/1/0.07)	7	90	3
8	**4e**	$PhCH_2$	PMB	OAc	MeCN-H_2O-EtOH (4/1/0.07)	7	—[e]	—

a) Carried out at 3.3 mA cm^{-2} with Pb plate (3 cm^2) cathode at room temperature. b) PMB: *p*-methoxybenzyl; SBT: 2-benzothiazolylthio. c) Unless otherwise noted, d.c. current was supplied until most of the starting materials **4** were consumed. d) Isolated yields after column chromatography. e) **4e** was recovered (96%).

and previous "Penicillin-Cephalosporin Conversion"[3] (Scheme 1) provides a new convenient route for synthesis of **5**.

Experimental

IR spectra were obtained on a JASCO IRA-1 grating infrared spectrophotometer. ^1H NMR spectra were recorded with a Hitachi R-24 spectrometer and chemical shifts are reported in part per million (δ) relative to tetramethylsilane (δ=0.0 ppm) as an internal standard in a $CDCl_3$ solution. C(3′)-Substituted cephalosporins **4a**, **4b** (X=Cl),[3] **4d** (X=SBT)[5] and **4e** (X=OAc)[5] were prepared by the reported procedure. Iodide **4c** (X=I) was prepared by treatment of **4a** with KI (1.2 equiv) and $NaHCO_3$ in refluxing acetone for 1 h.

General Procedure for Electrochemical Reductions. The electroreduction was carried out at room temperature in a H-shaped cell separated by fritted glass, which was fitted with lead cathode (3 cm^2) and platinum anode (3 cm^2). Regulated d.c. power was supplied by Metronix Galvanostat Model 543B. When the starting materials were almost consumed (3.5—7.0 F mol^{-1}), the electrolysis was terminated and the catholytes were worked up in the usual manner. The structual assignment of the products **5** and **6** were performed by comparison of the IR and ^1H NMR spectra with those of authentic samples.[2d] The conditions and results are summarized in Table 1. A typical electrolysis procedure is as follows.

Electroreduction of 4a (R^1=$PhCH_2$; R^2=*p*-CH_3O-$C_6H_4CH_2$; X=Cl) (Entry 1). A mixture of THF (12 ml) and H_2O (3 ml) containing $LiClO_4$ (330 mg) and NH_4ClO_4 (460 mg) was added into both the cathode and anode compartments (7.5 ml each) and **4a** (101 mg, 0.21 mmol) was added into the catholytes. The mixture was electrolyzed under stirring at 3.3 mA cm^{-2} for 1.4 h. The catholytes were concentrated in vacuo to ca. 2 ml and the residue was extracted with AcOEt. The extracts were combined, washed with brine, and dried (Na_2SO_4). Evaporation of the solvents followed by column chromatography on SiO_2 with hexane/AcOEt (5 : 1) afforded 2-methylenecepham **5a** (=**5c**) (R^1=$PhCH_2$; R^2=*p*-CH_3O-$C_5H_4CH_2$, 82 mg, 87%)[2d]: IR ($CDCl_3$) 3398, 3010, 1779, 1745, 1689, 1620, 1597, 1519, 1251 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.01, 3.43 (2H, AB q, *J*=14 Hz, CH_2S), 3.57 (3H, s, OCH_3), 3.76 (2H, s, CH_2), 5.04 (2H, s, CH_2), 5.12 (2H, s, H_2C=C), 5.21 (1H, d, *J*=4 Hz, CH (6)), 5.57 (1H, dd, *J*=4 Hz and 10 Hz, CH (7)), 6.80 (1H, d, *J*=10 Hz, NH), 7.10—7.41 (9H, m).

2-Methylenecepham **5b** (R^1=$PhCH_2$; R^2=$PhCH_2$)[2d]: IR ($CDCl_3$) 3398, 3000, 1768, 1742, 1680, 1510, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.07, 3.56 (2H, AB q, *J*=14 Hz, CH_2S), 3.48 (2H, s, CH_2), 5.03 (2H, s, CH_2), 5.12 (2H, s, H_2C=C), 5.20 (1H, d, *J*=4 Hz, CH (6)), 5.12 (1H, dd, *J*=4 Hz and 8 Hz, CH (7)), 6.78 (1H, d, *J*=8 Hz, NH), 7.10—7.41 (10H, m).

2-Methylenecepham **5d** (R^1=$PhOCH_2$; R^2=$PhCH_2$): IR ($CDCl_3$) 3390, 3010, 1775, 1744, 1681, 1610, 1590, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.06, 3.51 (2H, AB q, *J*=14 Hz, CH_2S), 4.50 (2H, s, CH_2), 5.14 (2H, s, CH_2O), 5.22 (2H, s, H_2C=C), 5.36 (1H, d, *J*=4 Hz, CH (6)), 5.66 (1H, dd, *J*=4 Hz and 10 Hz, CH (7)), 6.85 (1H, d, *J*=10 Hz, NH), 7.00—8.75 (10H, m).

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