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PROMINENT ASPECTS OF ELECTROORGANIC SYNTHESIS IN β-LACTAM CHEMISTRY

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ABSTRACT

The potentiality of electrolysis procedures in the penicillin-cephalosporin conversion as well as in the direct transform of penicillins into oxazoline-azetidinones as an intermediate for the preparation of the sulfur-free analogues of cephalosporins are discussed. Especially, a chemoselective electrolytic chlorination of methyl group of 3-methyl-3-butenoate moiety of thiazoline-azetidinone derived from penicillins, a direct synthesis of 3'-thiosubstituted cephalosporins from the thiazoline-azetidinones, an improved synthesis of exo-methylenecephams, an efficient route to 3-chloromethyl-Δ^3-cephems, electrochemical S-S bond fission of 4-(2-benzothiazolyldithio)azetidinones, a direct transformation of penicillins into oxazoline-azetidinones by chloride salt-promoted electrolysis, and a versatile intermediate for new β-lactam antibiotics are presented.

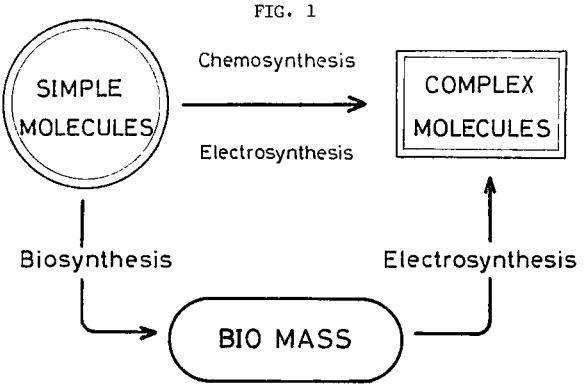
I. INTRODUCTION

Making complex molecules from simple molecules is a major feature of synthetic organic chemistry. Every synthetic conversions demand some of characteristic synthetic reagents. The synthesis by using a variety of chemical reagents might be called "Chemo-synthesis" (FIG. 1). Within the last decade, synthetically meaningful electrosynthetic methods have been developed and apparently some of them are going to replace chemo-synthetic methods. The current interests in the electrosynthesis are focused on the prominent aspects as bellows.

1) Pollution-free, less-energy and less-resources
2) Recycle use of reagents or mediators
3) Development of new reactions and new technologies based on its unique reaction circumstance
4) Manufacturing of chiral synthetic blocks from biomass

One of the recent topics on organic syntheses must be the synthesis of chiral molecules. The asymmetric synthesis is of course a hot subject in this line. Today, some of the attempts have been succeeded for this purpose, but still there are some difficulties to attain the natures ability. On the other hand, naturally occurring biomass must be important in obtaining chiral synthetic blocks. Actually, the utilization of the chiral biomass as a synthetic block becomes a current problem. Electrolysis procedure can be expected to be a powerful tool of the conversion of biomass to chiral synthetic blocks. The combination of electrosynthesis and biosynthesis will also provide a significant way to prepare chiral complex molecules in future.

FIG. 1



In order to clarify the potentiality of electrolysis procedures, we chose the penicillin-cephalosporin conversion problem, because it contains enough subjects to examine those four characteristic aspects of electrosynthesis.

The clinical demand of cephalosporin antibiotics is rapidly increasing lately because of their broad spectrum activities and their effectiveness to penicillin resistant strains. Those cephalosporins are chemically prepared from expensive 7-amino-cephalosporanic acid (7-ACA) by acylating the 7-amino group and replacing 3'-acetoxy group with suitable substituents. On the other hand, stimulated by the increased use of cephalosporins, many efforts have been made in the conversion of penicillins to cephalosporins. Especially, the synthesis of 3'-substituted cephalosporins has attracted much attention of many investigators, but still only a few successful reports have appeared.[1)]

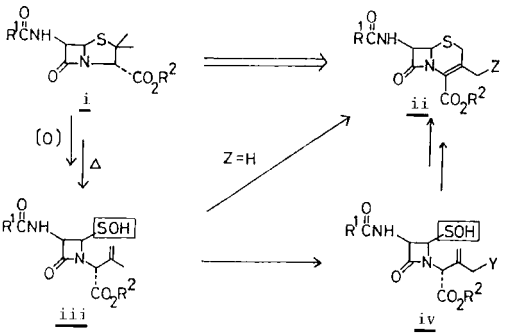
The first penicillin-cephalosporin conversion has been reported by Morin et al.[2)] which comprises oxidation of penicillin to its sulfoxide followed by thermolysis leading to sulfenic acid iii and recyclization of iii affording ii. Many improved methods for protection (or trap) of iii and the recyclization (i→iii→ii) has been developed. However, the cephalosporins so far obtained lack substituents at the C-3' position. In order to obtain 3'-substituted cephalosporin, the oxidative functionalization of the terminal allylic position, leading to intermediate iv is required (SCHEME I). In other words, the oxidative functionalization (iii→iv) is an essential step of the penicillin-cephalosporin conversion (Z ≠ H).

We found that electrolytic ene-type chlorination is a powerful tool for this purpose. Following discussion covers some of our recent electrochemical contribution on the penicillin-cephalosporin conversion as well as new β-lactam synthesis.

II. Chemoselective Electrolytic Chlorination of Methyl Group of 3-Methyl-3-Butenoate Moiety of Thiazoline-azetidinone Homologues[3)]

Thiazoline-azetidinones 1 derived from penicillins[4a)] are potential intermediates for the penicillin-cephalosporin conversion, in which the oxidative functionalization of the methyl group of the 3-methyl-3-butenoate moiety is an essential step. Recently, Cooper reported the direct chlorination of 1 with

SCHEME 1

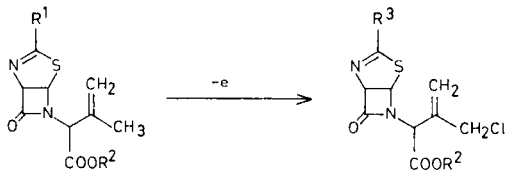


chlorine (25°C, 3 days) or t-butyl hypochlorite (~ 60% yields), giving the corresponding chlorinated compounds 2.[4b]

During our studies on halide salts promoted electrosynthesis[5] we found that electrolysis of 1 (R^1 = $PhCH_2$, $PhCCl_2$, $PhOCH_2$ and PhC=O) in two-phase systems (H_2O-CH_2Cl_2-Pt or C electrodes) provided chemoselective chlorination products 1g (R^1 = $PhCCl_2$), 2a, 2b, and 2f, depending on the amount of electricity passed as well as on the concentration of Cl^- in the media. Thus, a stirred mixture of thiazoline-azetidinone 1a (400 mg), NaCl (8g), and H_2SO_4 (0.5 ml) in H_2O (24 ml)-CH_2Cl_2 (20 ml) was electrolyzed by using platinum foil electrodes (anode 6 cm^2) in an undivided cell at a constant current (10 mA/cm^2), passing 15 F/mol of electricity, at room temperature. The usual workup followed by column chromatography gave 2a (R^3 = $PhCCl_2$, R^2 = Me) in 89% yield.

Likewise, the electro-chlorination of 1b-e proceeded smoothly, yielding the corresponding allylic chlorides 2b-d. The results are summarized in the TABLE 1. Carbon electrodes can be used without any disadvantage (entry 2). The effect of H_2SO_4 was remarkable, since the absence of H_2SO_4 resulted in a mixture of benzylic chlorides 1g (25%), 1h (20%), and recovered 1a (34%) together with complex compounds (20%) after passage of 15 F/mol of electricity. Particularly noteworthy is the fact that the two-phase electrolysis procedure brought about no appreciable amount of hydrolysis products on either the thiazoline or the β-lactam ring. In place of CH_2Cl_2, other hydrophobic solvents, e.g., $CHCl_3$ and AcOEt, could be used. In contrast to this, the use of hydrophylic solvents, e.g., THF, CH_3CN, CH_3CN-THF, or CH_2Cl_2-THF, even in a two phase system, facilitated hydrolysis of the thiazoline and/or the β-lactam ring, leading to the ring opened products 3 and/or 4.

In the course of electro-chlorination of 1b (R^1 = $PhCH_2$), leading to trichlorides 2b (entry 3) gem-dichloride 1c (89%) was obtained as an initial product at a higher concentration of sodium chloride (1g/3 ml) in water when 10 F/mol of electricity was passed (SCHEME 2). Electrolysis of the dichloride 1c in the same media afforded 2b in 85% yield (entry 4). The result is in contrast to that of the electrolysis at a lower concentration of aqueous sodium chloride (100 mg/3 ml), which gave rise to the competitive formation of benzylic and allylic chlorides 1c (9%), 1f (11%), 2e (10%), and 2f (11%).



1 2

TABLE 1[a)]

entry	substrate 1			electrolysis system	electricity F/mol	product 2		
		R^1	R^2				R^3	(Yield, %)[b)]
1	1a	$PhCH_2$	Me	H_2O-CH_2Cl_2-(Pt)	15	2a	$PhCCl_2$	(89)
2	1a	$PhCH_2$	Me	H_2O-CH_2Cl_2-(C)	15	2a	$PhCCl_2$	(82)
3	1b	$PhCH_2$	$PhCH_2$	H_2O-$CHCl_3$-(Pt)	25	2b	$PhCCl_2$	(76)
4	1c	$PhCCl_2$	$PhCH_2$	H_2O-$CHCl_3$-(Pt)	10	2b	$PhCCl_2$	(85)
5	1d	$PhOCH_2$	Me	H_2O-CH_2Cl_2-(Pt)	10	2c	$PhOCH_2$	(77)
6	1e	PhCO	Me	H_2O-CH_2Cl_2-(Pt)	5	2d	PhCO	(80)

a)Carried out at a constant current of 10 mA/cm^2 at room temperature.
b)Isolated yields.

SCHEME 2

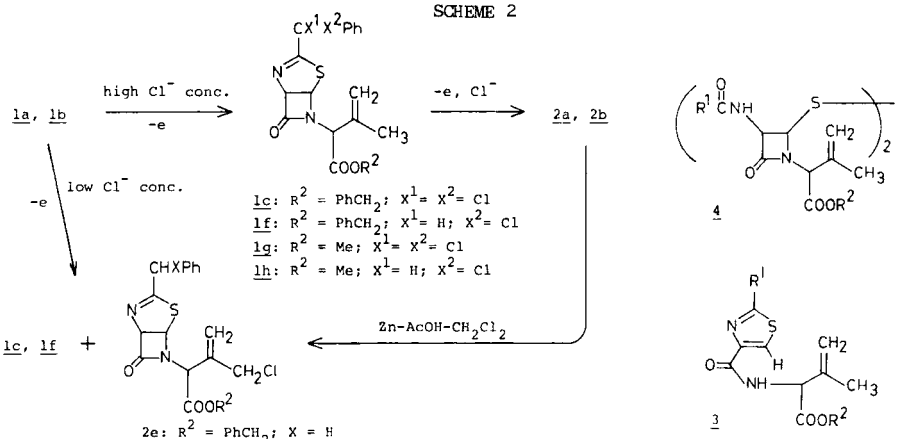
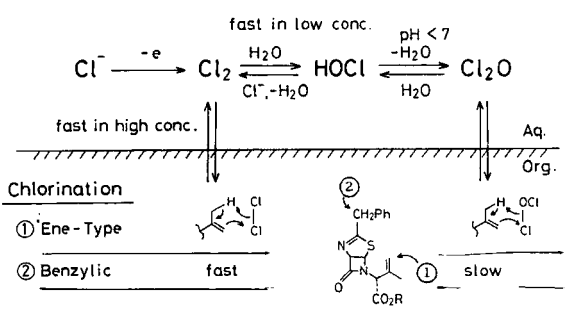


FIG. 2



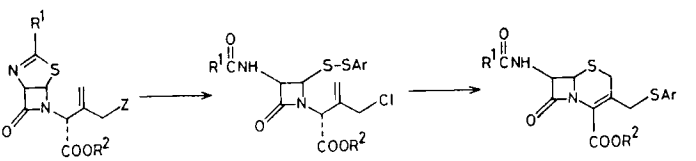
This change of the product distribution is due to the fact that the discharge of Cl^- can produce different chlorinating agents, e.g., Cl_2, HOCl, Cl_2O, etc., depending upon the Cl^- concentration, the pH of the media, oxidation potentials, and the presence of aprotic solvents.[6] As shown in FIG. 2, the discharge of chloride ion at the anode produces chlorine molecule, whose hydrolysis in an aqueous layer gives hypochloric acid, especially when the medium is keeping pH value as a weak acid and a low concentration of chloride ion. It is well known that generated hypochloric acid is in equilibrium with chlorine oxide (Cl_2O). Those chlorine and chlorine oxide would migrate into the organic layer and react with olefin to give the ene-type chlorination product.

Conversion of 2a and 2b (R^3=$PhCCl_2$) into the corresponding allylic chlorides 2e and 2g (R^3 = $PhCH_2$) can be achieved in over 90% yields by removal of the chlorine atoms attached to the benzyl carbon by treatment with zinc dust in AcOH-CH_2Cl_2 (1/4) at 0-2°C.

III. Direct Synthesis of 3'-Thiosubstituted Cephalosporins from Thiazoline-Azetidinones[7]

Most of clinically significant cephalosporin antibiotics possess a sulfenyl group at the C-3' position. They have been prepared by displacement of the acetoxy group of the corresponding 3'-acetoxycephalosporins. In the preceding paragraph, the electrolytic enetype chlorination of the thiazoline-azetidinones 1 derived from penicillin G and V has been shown to give potent intermediates 2 for the synthesis of 3'-substituted cephalosporins. We sought a direct route to 3'-thio-substituted cephalosporins 6 from 2. A possible approach for this goal must comprise the ring opening of 2 to disulfides 5 and subsequent base catalyzed ring closure accompanied with displacement of the allylic chlorine atom by the leaving thiolate (ArS^-)(SCHEME 3).

SCHEME 3



1: Z = H
2: Z = Cl

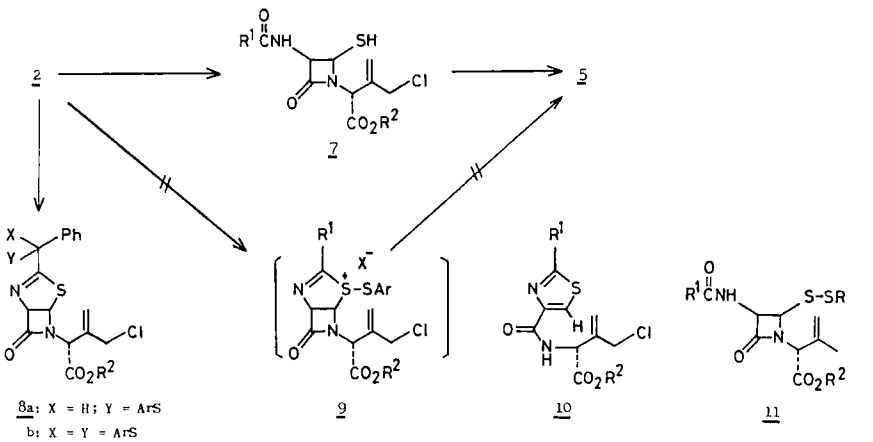
5

6

The conversion of 2 to 5 was accomplished by treatment with sulfenyl chloride in the presence of water. The thiazoline ring opening with sulfenyl chloride was a known reaction. The reaction of 1 (R^1 = $PhCH_2$; R^2 = p-NO_2PhCH_2) with $(CH_3)_2CHCH_2SCl$ affording the corresponding disulfide 11 has been reported.[8] However, there was no example with aromatic or heteroaromatic sulfenyl chloride. Recently, another attempt to synthesize the disulfide 11 by the reaction of 1 with sulfenyl iodide has been also reported but only trace amount of 11 was detected.[9] In fact, treatment of 2 with sulfenyl chloride in dioxane in the presence of water afforded the desired disulfide 5. However, the

yields were not satisfactory (∿ 20%) and we intended to clarify in details the reaction of 2 with aromatic and heteroaromatic sulfenyl chloride. In the reaction of thiazoline-azetidinones with sulfenyl halide, thiosulfonium halide like 9, has been always proposed at the initially formed intermediate (SCHEME 4). However, when the reaction of 2 with sulfenyl chloride was carried out in dry media and then quenched with water, no ring opened products but considerable amounts of sulfenylated products 8a and/or 8b were obtained (∿ 80% yields). The alternative reaction pathway is the first hydrolysis of thiazoline ring to give thiol 7 which is trapped with the sulfenyl chloride to yield the disulfide 5. In fact, when 2 was treated with aqueous HCl and subsequently with aromatic or heteroaromatic sulfenyl chloride, the desired disulfides 5 were obtained in quite satisfactory yields as shown in the TABLE 2.

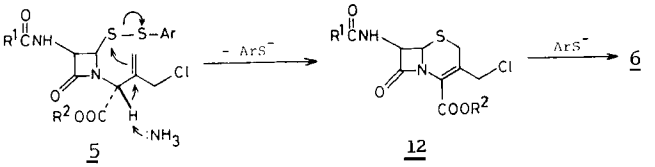
SCHEME 4



The ring closure of the disulfide 5a was widely examined by using acids, bases, halogens, and so on. We finally found that a combination of gaseous ammonia (NH_3) and dimethylformamide (DMF) achieved the task. Thus, the treatment of the disulfide 5a (0.07 mmol) with NH_3 (∿ 0.14 mmol) in DMF (0.8 ml) at -30∿-25°C for 60 min afforded the desired 3'-benzothiazolylthiocephalosporin 6a. The choice of a base is important, because stronger base such as triethylamine which abstracts the proton faster than ammonia gave us unsatisfactory results.

Interestingly, the reaction of 5b ($R^1 = R^2 = PhCH_2$, $Ar = C_6Cl_5$) with ∿ 1.5 equiv. of NH_3 in DMF (∿ -25°C, 60 min) afforded a mixture of 6b (35%) and 3'-chlorocephalosporin 12 ($R^1 = R^2 = PhCH_2$, 27%). The use of more than 2 equiv. of NH_3 resulted in an exclusive formation of 4b. This suggests that the ring closure and the thio-substitution proceed stepwise (SCHEME 5) and 3'-chlorocephalosporin 5 is an intermediate.

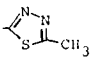
SCHEME 5



5 12

TABLE 2

	R^1	R^2	Ar[a]	yield, %[b] 5	6
a	$PhCH_2$	$PhCH_2$	BT	81	74
b	$PhCH_2$	$PhCH_2$	DZ	70	83
c	$PhCH_2$	$PhCH_2$	C_6Cl_5	74	83
d	$PhCH_2$	CH_3	BT	61	64
e	$PhOCH_2$	$PhCH_2$	BT	84	83
f	$PhOCH_2$	$PhCH_2$	DZ	65	88
g	$PhOCH_2$	$PhCH_2$	C_6Cl_5	74	88

a) BT =  ; DZ = 

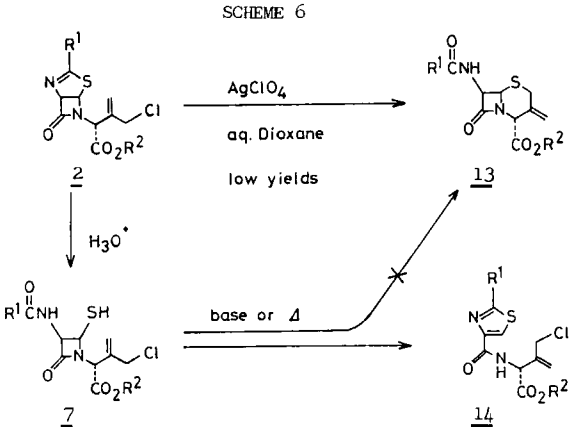
b) Isolated yields.

IV. Improved synthesis of Exomethylenecephams

Exomethylenecephams 13 are useful synthetic intermediates for various new types of cephalosporin antibiotics. For example, by the ozonolysis of the exomethylene double bond, they have been derived to cephems which have a substituent directly attached to the C-3 position.

The electrochemically produced chlorothiazoline-azetidinones 2 can be good precursors of the exomethylenecephams 13 since Uyeo succeeded in the conversion of 2 into 13 by the treatment with silver perchlorate although the yield was unsatisfactory.[10] So we intended to develop a new and more practical method to convert 2 into 13 (SCHEME 6).

SCHEME 6



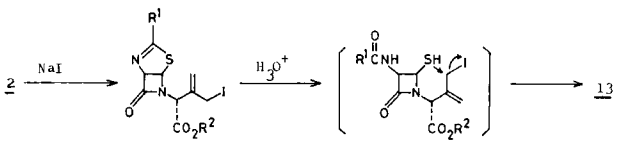
2 13 7 14

It has been demonstrated that the thiol 7 can be generated by the hydrolysis of 2. The intramolecular substitution of the allylic chlorine atom by the thiol in 7 would be the straightforward route to the exomethylenecephams 13. Surprisingly, there has been no such conversion of 7 into 13, so we investigated this possibility.

Variety of conditions and bases have been examined to the thiol 7, but only identified product was thiazole 14. These failure made us believe that the allylic chloride is not reactive enough for the substitution. Consequently, we tried to use iodide instead of chloride.

The allylic iodide 15 was readily prepared from the chloride 2 with sodium iodide in acetone. The acid catalyzed hydrolysis of the iodide 15 afforded the expected exomethylenecepham 13. Although 16 was not isolated, the ring closure would proceed via 16 at room temperature without any bases due to the high reactivity of the iodide 15.

SCHEME 7



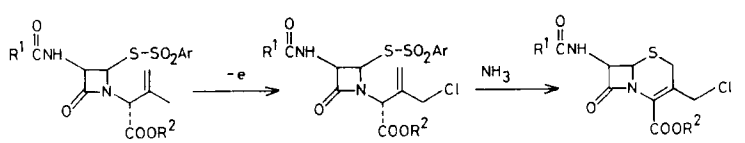
15 16

V. An Efficient Route to 3-Chloromethyl-Δ^3-Cephems[11]

As another application of the electrolytic ene-type chlorination, we developed a straightforward synthetic route to 12 from azetidinone 17, prepared from natural penicillins.[12] 3-Chloromethyl-Δ^3-cephems 12 are important precursors in the synthesis of 3'-substituted cephalosporin antibiotics. They have been prepared by displacement of the acetoxy group of 3-acetoxymethyl cephalosporins with chlorine atom.[13]

The conversion of 17 to 12 comprises the electrolytic ene-type chlorination[5] of 17 and the ring closure of 18 with base (SCHEME 8). It was found that the arenesulfonyl groups (Ar-SO_2) have a sufficient nature for both protecting the thiol groups at C(4)-position in electrolysis conditions (17→18)

SCHEME 8



17 18 12

and playing the part of leaving groups in cyclization conditions (18→12). Some of our results are summarized in the TABLE 3.

The ring closure of 18a (0.1 mmol) was accomplished by treatment with NH_3 (gas, 0.3 mmol) in DMF (0.5 ml) at -20 ∿ -30°C for 1h, yielding 12a (R^1 = $PhCH_2$, R^2 = Me, 74%) without contamination of the Δ^2-isomer. Use of gaseous ammonia was most effective for the cyclization among the following bases (yields of 12a): AcONa (29%) Et_3N (18%): KOH (17%): and KI (14%).

TABLE 3

entry	R^1	R^2	Ar	yields, %[a] 17→18	18→12
1	$PhCH_2$	CH_3	p-NO_2Ph	83	74
2	$PhCH_2$	CH_3	Ph	77	82
3	$PhCH_2$	$PhCH_2$	p-NO_2Ph	91	86
4	$PhCH_2$	$PhCH_2$	Ph	84	78
5	$PhCH_2$	p-NO_2PhCH_2	p-NO_2Ph	75	52
6	$PhOCH_2$	$PhCH_2$	p-NO_2Ph	94	93

a) Isolated yields after column chromatography (SiO_2).

VI. Electrochemical S-S Bond Fission of 4-(2-Benzothiazolyldithio)azetidinones (Kamiya's Disulfides)

In connection with penicillin-cephalosporin conversion, disulfides 19, readily accessible from natural penicillins by Kamiya's method,[14a] are one of most actively investigated intermediates. Namely, by the action with bromine or $CuCl_2$ in CH_2Cl_2, the disulfides 19 can be converted to the corresponding 2β-halomethylpenicillins 20 (X = Br, Cl), which are good precursors of useful cephalosporin antibiotics.[14] In fact, the electrolytic cleavage of the S-S bond of 19 was found to be a good method for the conversion of 19 to either 2-halomethylpenicillins 20, 3-halocephams 21 or 4-methoxysulfinyl-azetidinone derivatives 25.[15]

The electrolysis was carried out in an undivided cell fitted with two Pt electrodes. A solution of the disulfide 19a (R^1 = $PhCH_2$, R^2 = CH_3) in CH_3CN-tetrahydrofuran-H_2O (6/1.5/0.3) in the presence of halide salts at 10 mA/cm^2 at 23-27°C. After passage of 4 F/mol of electricity, the usual workup gave halopenicillins 20 and halocephams 21 along with bis(2-benzothiazolyl)disulfide. Some of the results are summarized in the TABLE 4.

Among various kinds of bromide salts, $MgBr_2$ was most effective for this purpose (entry 1). Thus, use of alkaline metal salts, e.g., LiBr, NaBr, and KBr or HBr in place of $MgBr_2$ afforded a mixture of 20a and 21a (R^1 = $PhCH_2$, R^2 = CH_3, X = Br) in 73-46% yields (entries 2-5), while ammonium bromides are ineffective, affording only dimer 24 and/or decomposition products (entries 6 and 7). In contrast to the reported results,[15] electrolysis of 19a with $MgCl_2$ in the same medium brought about the exclusive formation of the corresponding

chloropenicillin 20b ($R^1 = PhCH_2$, $R^2 = CH_3$, X = Cl, entry 8). However, iodide salts, e.g., MgI_2 and NaI are less effective, leading to a small amount of iodocepham 21c ($R^1 = PhCH_2$, $R^2 = CH_3$, X = I, ∿ 20%) along with dimer 24 (26-41%) (entries 9 and 10). The electrolytic conversion of 19a to 20b could be achieved by using two-phase electrolysis system, comprising aqueous chloride salts and CH_2Cl_2 (entries 11 and 12), which are the typical electrolysis system for

SCHEME 9

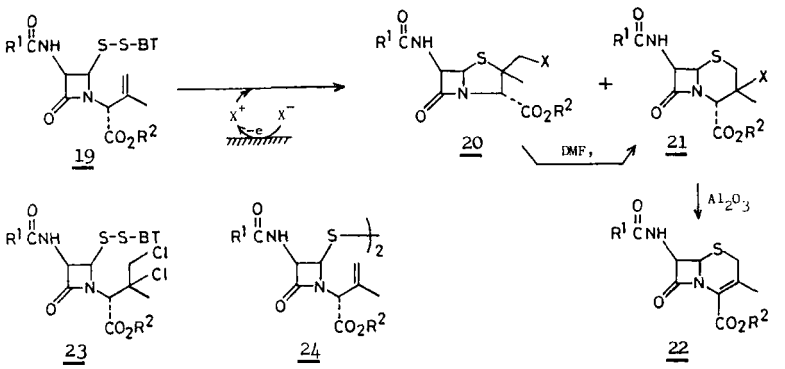


TABLE 4[a)]

entry	halide salt[b)]	solvents[c)]	products, yields %[d)]			
			20 + 21 (20/21)	23	24	19
1	$MgBr_2$	A	96 (54/46)	--	--	--
2	LiBr	A	73 (38/62)	--	--	18
3	NaBr	A	74 (35/65)	--	--	22
4	KBr	A	58 (50/50)	--	25	21
5	HBr	A	46 (65/31)	--	--	14
6	Et_4NBr	A	--	--	--	15
7	NH_4Br	A	--	--	52	32
8	$MgCl_2$	A	66 (100/0)	--	--	15
9	NaI	A	20 (0/100)	--	41	14
10	MgI_2	A	trace	--	26	68
11	NaCl	B	72 (100/0)	5	--	26
12	$MgCl_2$	B	65 (100/0)	--	--	30
13	NaBr	B	--	--	--	90
14	NaI	B	--	--	--	100

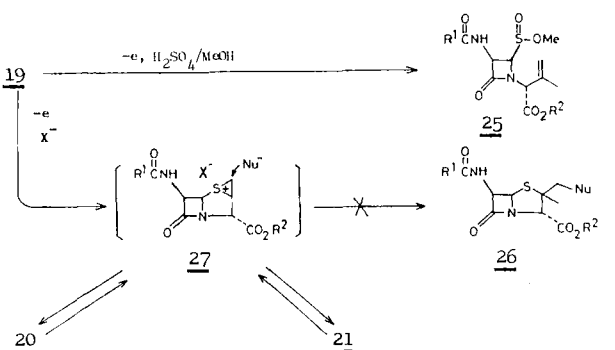
a) Carried out at 10 mA/cm^2, passing 4 F/mol of electricity, at 23-27 °C. b) A stoichiometric amount of halide salts was added. c) A: $CH_3CN/THF/H_2O$ (6/1.5/0.3); B: CH_2CH_2/H_2O (5/3). d) Isolated yields after column chromatography (SiO_2, benzene/AcOEt: 5/1).

the ene-type chlorination described in the preceding sections. Similar attempts with bromide salts and iodide salts in the two-phase electrolysis system failed (entries 13 and 14).

Apparently, the product ratio of halopenicillins 20 to halocephams 21 varied remarkably depending on the choice of halide salts as well as the electrolysis conditions. The ratio of 20a to 21a (X = Br) was also effected by the employed temperature as follows : temperature, 20a/21a (total yields): 23-25°C, 54/46 (96): 5-9°C, 80/20 (100): -3 ∿ -5°C, 88/12 (90). The results so far obtained suggest that in the initial stage of the electrolysis, kinetically favored halopenicillins 20 (X = Br, Cl, and I) are formed via episulfonium ion 27 (SCHEME 10) by the action with the anodically generated X^+ or X_2 (X = Br, Cl, and I) in a similar fashion to the reported chemical conversion.[14a] Then, the isomerization of 20 (X = Br and I), having a good leaving group at the C-2' position, to 21 would take place in the electrolysis media and partly under the workup conditions. However, the chloropenicillin 20b (X = Cl) would be stable enough in the electrolysis media to be recovered intact. The transformation of 20a (X = Br) into 21b could be performed by standing in N,N-dimethylformamide at room temperature overnight[14a] and subsequent chromatography on a Al_2O_3 column with benzene/AcOEt (1/1) afforded desacetoxycephalosporin 22 ($R^1 = PhCH_2$, $R^2 = CH_3$, 95%).

With regard to the isomerization (20→27→21) in the aqueous medium, it is notable that the solvolyzed products 26 (Nu = OH and $NHCOCH_3$) could not be detected, which are expected to be generated by the attack of the solvent to 27. Several attempts to trap the intermediate 27 by using aqueous or protic solvents, e.g., aqueous acetone, aqueous THF, aqueous DMF, and methanol, failed, but the electrolysis of 19a (0.5 mmol) in methanol (50 ml) containing conc. H_2SO_4 (0.4 ml) afforded 4-methoxysulfinylazetidinone 25 ($R^1 = PhCH_2$, $R^2 = CH_3$, 53%), which is a new class of intermediates for β-lactam antibiotic synthesis.

SCHEME 10

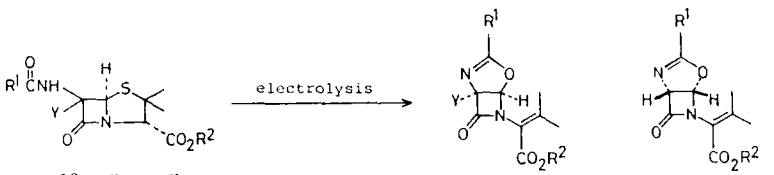


VII. A Direct Transformation of Penicillins into Oxazoline-Azetidinones by Chloride Salts-Promoted Electrolysis

The sulfur-free analogues of penicillins and cephalosporins have attracted much attention of both synthetic and medicinal chemists, since the successful development of new 1-oxacephem antibiotics was made by Shionogi group.[16] Namely, oxazoline-azetidinone derivatives 29 and 30 have been frequently used as a key intermediate in the synthetic chemistry of the new β-lactam antibiotics.[17] The compounds 29 and 30 have been usually prepared by two-step operation, involving the reaction of 19 and 28 with chlorine or t-butylhypochlorite followed by treatment with base.

We found that the direct conversion of penicillins 19 and 28 into the corresponding oxazoline-azetidinones 29 and 30 can be achieved by the halide salt-mediated electrolysis. The electrolysis was carried out in an undivided cell fitted with two Pt electrodes. The electrolysis conditions and results are summarized in the TABLE 5. The temperature (-70°C) is critical in this transformation (entry 1), since the electrolysis at -40 ∿ 0°C brought about a considerable amount of the ring-opening products on the β-lactam ring, affording only

SCHEME 11



19a: Y = α-H
b: Y = β-H
28: Y = α-OCH_3

29a: Y = H
30: Y = OCH_3

29b

TABLE 5[a]

entry	penicillin	Y	R^1	R^2	electrolysis system[b]	temp °C	current F/mol	product (yield, %)[c]
1	19a	α-H	$PhCH_2$	CH_3	A	-70	3	29a (82)[d]
2	19a	α-H	$PhCH_2$	CH_3	A	-40	3	29a (45)
3	19a	α-H	$PhCH_2$	CH_3	A	0	3	29a (20)
4	19a	α-H	$PhCH_2$	CH_3	B	-40	5	29a (81)
5	19a	α-H	$PhCH_2$	$PhCH_2$	B	-40	5	29a (65)
6	19a	α-H	$PhOCH_2$	CH_3	B	-40	5	29a (74)
7	19a	α-H	Ph	CH_3	B	-40	5	29a (72)
8	19a	α-H	Ph	Ph_2CH	B	-40	5	29b (93)
9	28	α-OCH_3	$PhCH_2$	CH_3	C	0	5	30 (71)
10	19b	β-H	$PhCH_2$	CH_3	B	-40	6	29b (80)[e]

[a] Carried out at 10 mA/cm^2 by using Pt electrodes. [b] A: LiCl (0.19 mmol)-methanol (2 ml)-t-butyl alcohol (0.5 ml); B: $MgCl_2$ (0.2 mmol)-methanol (2.5 ml)-t-butyl alcohol (0.5 ml); C: $MgCl_2$ (0.1 mmol)-methanol (2 ml)-tetrahydrofuran (0.5 ml). [c] Isolated yields after column chromatography. [d] $[\alpha]_D^{25}$ = +49° (c 0.1 in $CHCl_3$; lit.[9] +46°). [e] $[\alpha]_D^{25}$ = -44° (c 0.1 in $CHCl_3$)

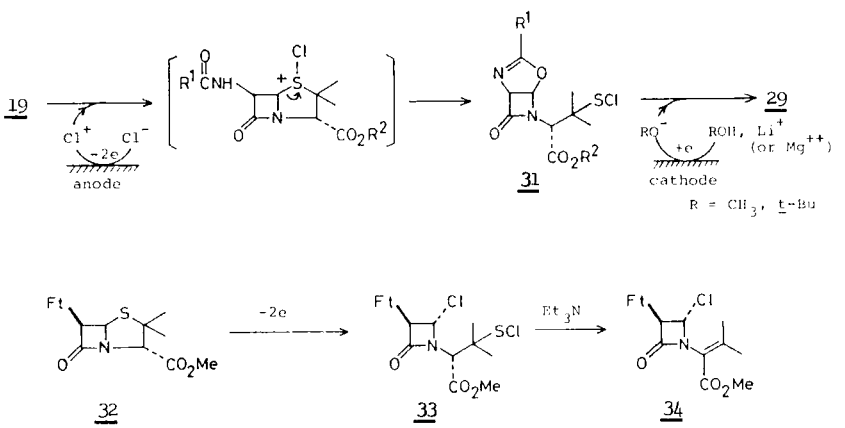
45-20% yields of 29a (entries 2 and 3). In contrast, use of $MgCl_2$ in place of LiCl provided good results even at -40°C, affording 29a in 81% yield (entry 4). In a similar manner, some of penicillins 19a and 28 were converted into the corresponding oxazoline-azetidinones 29a and 30 by using $MgCl_2$ at -40°C, smoothly (entries 5-9). 6-Epi-penicillin 19b (Y = β-H; $R^1 = PhCH_2$; $R^2 = CH_3$) was also converted to epi-oxazoline-azetidinone 29b ($R^1 = PhCH_2$; $R^2 = CH_3$, 80%) (entry 10).

The electrolytic transformation of 19 into 29 can be reasonably explained by assuming that the C(5)-S bond cleavage is promoted by the attack of Cl^+ (or Cl_2), generated by discharge of Cl^- at the anode, and the subsequent replacement with the amide oxygen gives oxazoline-azetidinone 31 which, in turn, suffers from desulfurization by the action with base (CH_3O^- or t-BuO^-) produced at the cathode (SCHEME 12). In fact, oxazoline-azetidinone 31 could be isolated when the electrolysis was carried out in an acidic medium. Thus, the electrolysis of 19a (Y = α-H; $R^1 = PhCH_2$; $R^2 = CH_3$, 0.31 mmol) in chloroform-3M hydrochloric acid (2.5 ml/0.5 ml) containing benzyltrimethylammonium chloride (0.15 mmol) at 0°C at 10 mA/cm^2, 2.5 F/mol of electricity passed, afforded 31 ($R^1 = PhCH_2$; $R^2 = CH_3$). Treatment of 31 with lithium methoxide in tetrahydrofuran at -70°C gave 29a (Y = H; $R^1 = PhCH_2$; $R^2 = CH_3$) in 60% yield from 19a.

Upon the electrolysis in the acidic media, 6-phthalimidopenicillin 32, which may be difficult in producing the oxazoline system, afforded azetidinone 33 and subsequent treatment of 33 with triethylamine gave 34 in 70% overall yield from 32.

In this electrochemical conversion of 19 and 28 into 29 and 30, both anodic and cathodic reactions, so called "paired reaction", proceed smoothly at the same time. It is possible only in the heterogeneous electrolysis system.

SCHEME 12

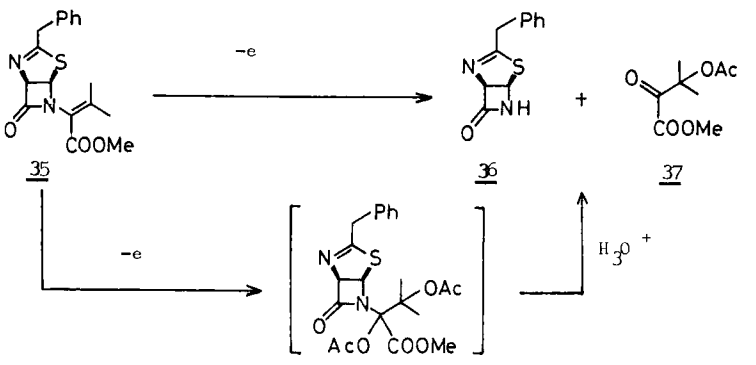


VIII. A Versatile Intermediate for New β-Lactam Antibiotics

Thiazoline-azetidinone 36 is a versatile intermediate for the synthesis of varieties of β-lactam antibiotics.[18] The most straightforward route to 36 must be removal of the β-lactam N-substituents of thiazoline-azetidinone 35, which is readily obtained from penicillins by Cooper's method.[4a] This has been usually done by the two-step operation, involving ozonolysis and the subsequent methanolysis.[19] Direct transformation of 35 to 36 has been also achieved by oxidation with potassium permanganate or osmium tetraoxide, but yields were unsatisfactory (∿ 37%).[20]

We found that the electrochemical acetoxylation of 35 proceeds smoothly, affording 36 along with 37.

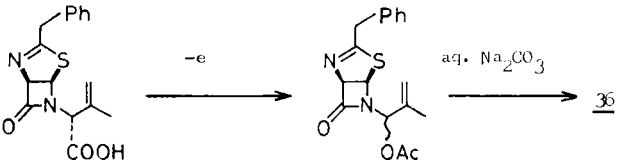
SCHEME 13



The electrolysis was carried out in a Et_3N-AcOH-EtOAc-Ac_2O-(Pt-Cu) system and 36 was obtained in 94% yield (∿ 60% conversion) together with the acetoxy-ester 37. This reaction can be reasonably explained by assuming that the electroacetoxylation of 35 gives intermediate 38 which is hydrolyzed either during the reaction or workup to afford 36. The intermediacy of 38 is implied by the isolation of the acetate 37.

Alternative electrochemical route to the thiazoline-azetidinone 36 was also developed. Carboxylic acid 39 prepared from penicillin G was converted to 36 via 40 by electrochemical decarboxylative acetoxylation followed by hydrolysis. After 4 F/mol of electricity was passed in AcONa-AcOH-DME-(C) system at 0°C, most of the starting material disappeared on TLC and the acetate 40 was obtained in 80% yield. Cooper, et al., reported that this acetate 40 could be obtained by lead tetraacetate oxidation of 39 and it was hydrolyzed in a buffer solution but he revealed the yield of 36 was low.[19] After various hydrolysis conditions of 40 were checked, the best result was achieved by adding aqueous sodium carbonate slowly to the methanol solution of 40, affording 36 in 69% yield.

SCHEME 14



39 40

REFERENCES

1. (a) G. Franceshi, M. Foglio, P. Masi, A. Suarato, G. Palamidessi, L. Bernardi, F. Arcamone, and G. Cainelli, J. Am. Chem. Soc., 99, 2848 (1977); (b) G.A. Koppel and L.J. McShane, ibid., 100, 288 (1978); (c) S. Uyeo, T. Aoki, H. Itani, T. Tsuji, and W. Nagata, Heterocycles, 10, 99 (1978).
2. R.B. Morin, B.C. Jackson, R.A. Mueller, E.R. Lavgnino, W.B. Scanlon, and S.L. Andrews, J. Am. Chem. Soc., 85, 1896 (1963).
3. S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, Tetrahedron Lett., 22, 3193 (1981).
4. (a) R.D.G. Cooper and F.L. José, J. Am. Chem. Soc., 92, 2575 (1970); (b) R.D.G. Cooper, Tetrahedron Lett., 21, 781 (1980).
5. S. Torii, K. Uneyama, T. Nakai, and T. Yasuda, Tetrahedron Lett., 22, 2291 (1981).
6. G. Valensi, E. Deltombe, N. de Zoubov, C. Vanleugenhagehe, and M. Pourbaix, "Atlas of Electrochemical Equilibrium in Aqueous Solutions", M. Pourbaix, Ed., Pergamon Press, Oxford, 1966; p 590.
7. S. Torii, H. Tanaka, M. Sasaoka, N. Saitoh, T. Siroi, and J. Nokami, Tetrahedron Lett., 23, 2495 (1982).
8. W.G.E. Underwood, Ger. Offen., 2303889 (1973): Chem. Abstr., 79, 105249 (1973).
9. R.G. Micetich, R.A. Fortier, and J. Liew, Can. J. Chem., 59, 1020 (1981).
10. S. Uyeo, T. Aoki, H. Itani, T. Tsuji and W. Nagata, Heterocycles, 10, 99 (1978).
11. S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, Tetrahedron Lett., 23, 2187 (1982).
12. J. Gosteli, Chemia, 30, 13 (1976).
13. (a) S. Karady, L.M. Sletzinger, Tetrahedron Lett., 2404 (1976); (b) H. Yazawa, H. Nakamura, K. Tanaka, and K. Kariyone, ibid., 3991 (1974) and references cited therein.
14. (a) T. Kamiya, T. Teraji, Y. Saitoh, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetrahedron Lett., 3001 (1973); (b) Y. Hamashima, S. Yamamoto, S. Uyeo, M. Yoshioka, M. Murakami, H. Ona, Y. Nishitani, and W. Nagata, ibid., 2595 (1979); (c) R.G. Micetich and R.B. Morin, "Recent Advances in the Chemistry of β-lactam Antibiotics", Ed. by J. Elks, Chem. Soc. Burlington House, London, 1977, p. 232.
15. Recently, electrolysis of 1 in a $(CH_3)_4NBr$-$ClCH_2COOH$-aq. CH_3CN (Pt electrodes) system, providing 3 (X = Br) in 18-45% yield has been reported. The electrolytic conversion of 1 into 2 (X = Cl) has been also attempted by using chloride salts, but has not yet been realized: A. Balsamo, P. Benedini, I. Giorgi, B. Macchia, and F. Macchia, Tetrahedron Lett., 23, 2991 (1982).
16. M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi, and W. Nagata, Tetrahedron Lett., 21, 353 (1980).
17. "Topics in Antibiotic Chemistry", S. Sammes, Ed., Ellis Horwood, Chichester, Vol. 4, 1980.
18. "Topics in Antibiotic Chemistry", Vol. 4, Ed. by P.G. Sammes, John Wiley & Sons, N.Y., 1980, p. 121.
19. R.C.G. Cooper, F.L. José, J. Am. Chem. Soc., 94, 1021 (1972).
20. For example, (a) E.C. Brain, A.J. Eglington, J.H.C. Nayler, M.J. Peason, and R. Southgate, J.C.S. Chem. Comm., 1972, 229; (b) idem., J.C.S. Perkin I, 1976, 447.