RECENT ADVANCES IN THE SYNTHESIS OF 7-METHOXYCEPHALOSPORINS (CEPHAMYCINS)

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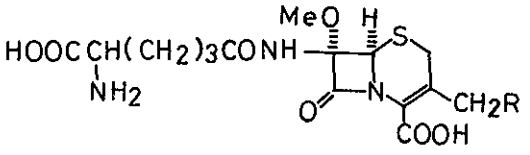
The various methods for introduction of a methoxy group at the seven posion of cephalosporin nucleus are reviewed based on our recent progress.

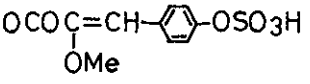
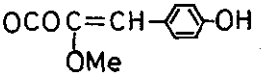
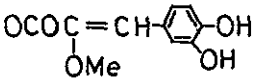
I. Introduction
II. Syntheses of 7α-methoxycephalosporins through a 7-imino system
III. Syntheses of 7α-methoxycephalosporins through a 7-anion system
IV. Conclusion

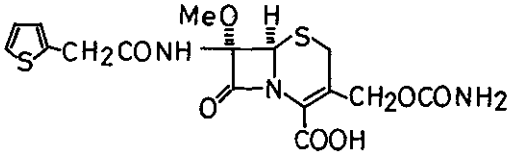
I. Introduction

Almost seven years have passed since isolation and structural elucidation of natural 7-methoxycephalosporins (cephamycins) have been disclosed by Lilly's[1] and Merck's[2] groups. Since then several variants have been also isolated by Japanese chemists.[3,4,5,6,7] Because of their enhanced activity against gram negative bacteria

7α-Methoxycephalosporins of Natural Origin



		R
Cephamycin	A [2]	
Cephamycin	B [2]	
Cephamycin	C [1,2,3]	$OCONH_2$
A-16884 [1]		OCOMe
C-2801 X [4]		
WS-3442 D [5]		H
SF-1623 [6]		SSO_3H
Y-G19ZD3 [7]		OH



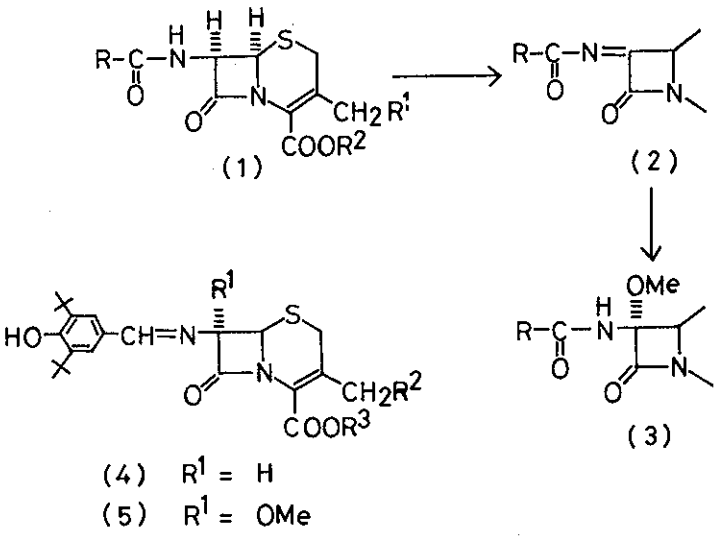
Cefoxitin

and cephalosporinase[8] as compared with the 7-H-cephalosporins, cephamycins have attracted the much attention of chemists and pharmacologists. If derivatives of cephamycins such as cefoxitin will be launched into clinical use[9] they will become a third type of β-lactam antibiotics succeeding to penicillins and cephalosporins while the forth type of candidates such as nocardicins,[10] clavulanic acid[11] and thienamycins[12] is in active progress.

Merck's acyl exchange reaction of cephamycin-C at the 7β-position[13] is valuable when a desired acid chloride is easily prepared and stable, while some difficulty is encountered in the case of an unstable carboxylic acid chloride or a polyfunctionalized acid whose acid chloride can not be synthesized. Then much effort has been made in the studies on introduction of a methoxy group at the 7α-position of cephalosporins which were obtained by fermentation of cephalosporium species as cephalosporin-C or by a ring expansion reaction of a penicillin S-oxide.[14]

II. Syntheses of 7α-methoxycephalosporins through a 7-imino system

Discoveries of t-butylhypochlorite method by Baldwin and Lilly's groups,[15] and Merck's chemists[16] for the introduction of methoxy functionality at the 7α-position starting from 7α-acylaminocephalosporins gave a striking contribution to a synthesis of 7α-methoxycephalosporins (3). Thereafter an elegant method was developed starting from the Shiff base (4) of 3,5-di-t-butyl-4-hydroxybenzaldehyde with a 7-aminocephalosporin which was



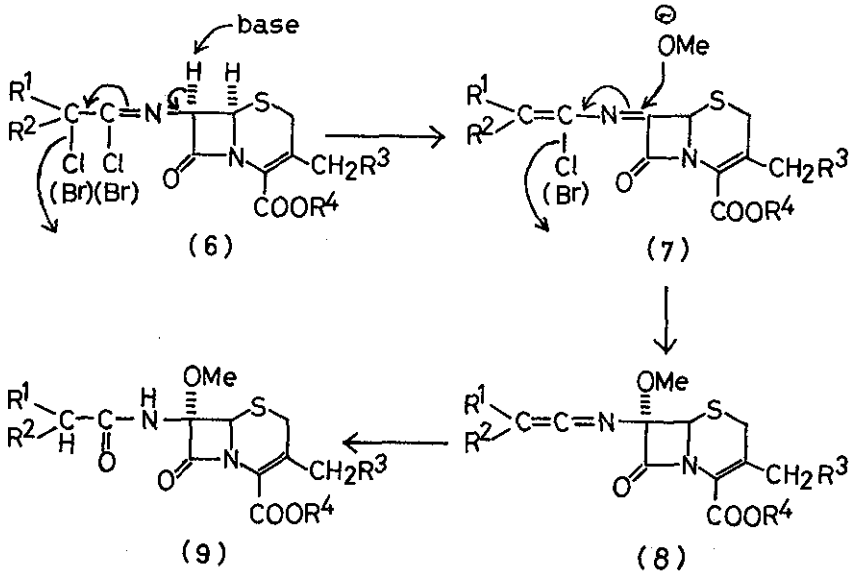
(1) (2) (3)

(4) R^1 = H

(5) R^1 = OMe

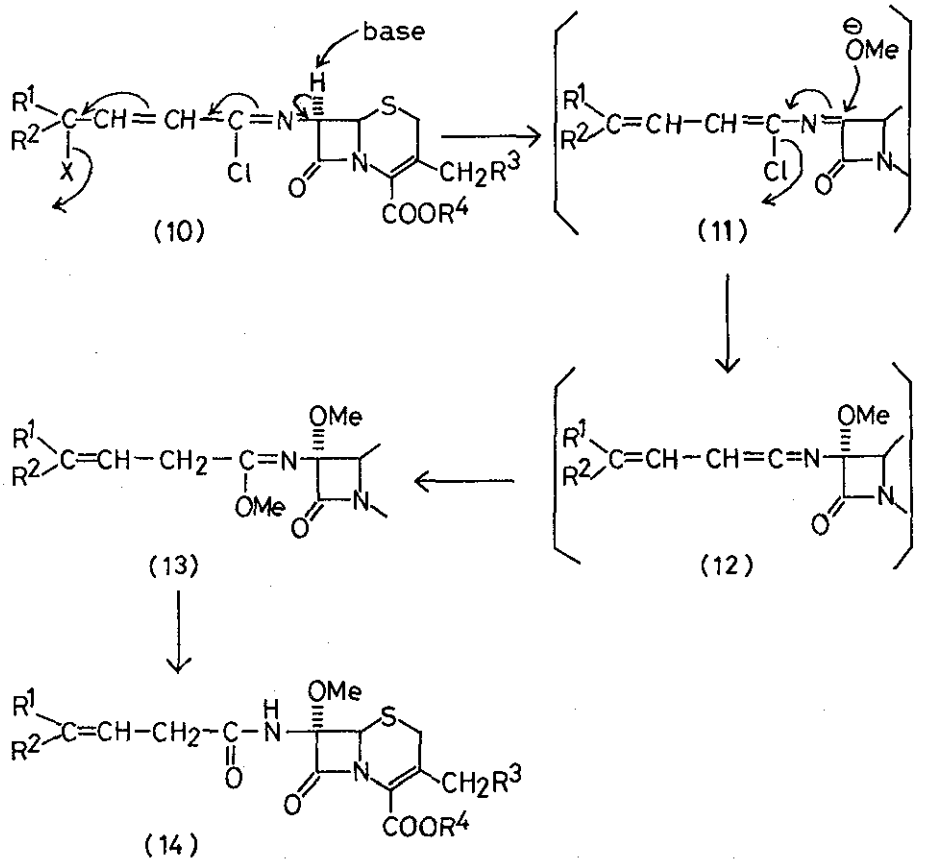
oxidized to a 7-iminobenzoquinone derivative with lead dioxide, followed by the addition of methanol to afford the 7α-methoxy-cephalosporins (5).[17]

Our first device for obtaining a 7-iminocephalosporin system is based on 1,4-elimination of the imino chloride (6) to give (7) which is methoxylated leading to the methoxyketenimine (8).[18] This ketenimine (8) is easily converted to the corresponding amide (9) on treatment with trifluoroacetic acid.[18] In some cases during methoxylation step excess lithium methoxide attacks the methoxyketenimine (8) to furnish a methoxyiminoether, which is also transformed to the amide (9) by the reaction with trimethylsilyl chloride and work-up with water.[18] There are two routes leading to the dihalo compound (6), one is starting from an α-halogenoacetamide which is chlorinated with phosphorus pentachloride according to a popular method[14] in the β-lactam chem-

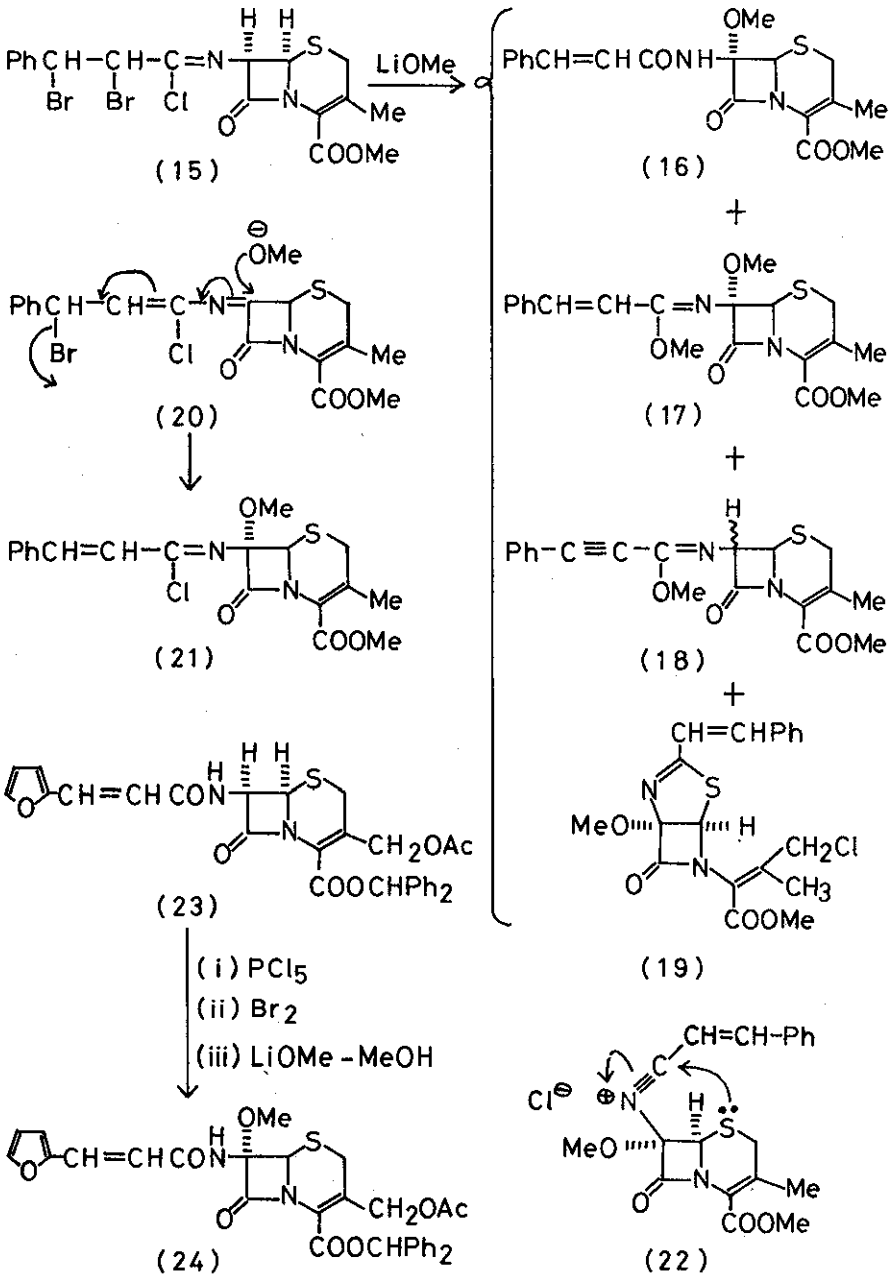


istry, another route is halogenation of a 7H-ketenimine which is brominated in the ketenimine part in preference to the 1 or 2 position of cephalosporin nucleus.[19] This 1,4-elimination reaction is successfully extended to a 1,6-eilimination. Thus, treatment of the imino chloride (10) with excess lithium methoxide gives the methoxylated iminoether (13). The iminoether (13) is converted into the desired amide (14) on treatment with trimethylsilyl chloride.[20] This result suggests that [1,(2n+2)]-elimination(n=an integer) would be amply applicable for methoxylation reaction starting from an ω-halogeno-conjugated iminochloride.

When the α,β-dihalogeno-iminochloride (15) is treated with excess lithium methoxide at -70° a 1,4-elimination reaction takes place in a slightly different way to give the methoxy amide (16) together with minor products, (17), (18), and the rearranged product (19).[21] In this reaction investigation of intermediates

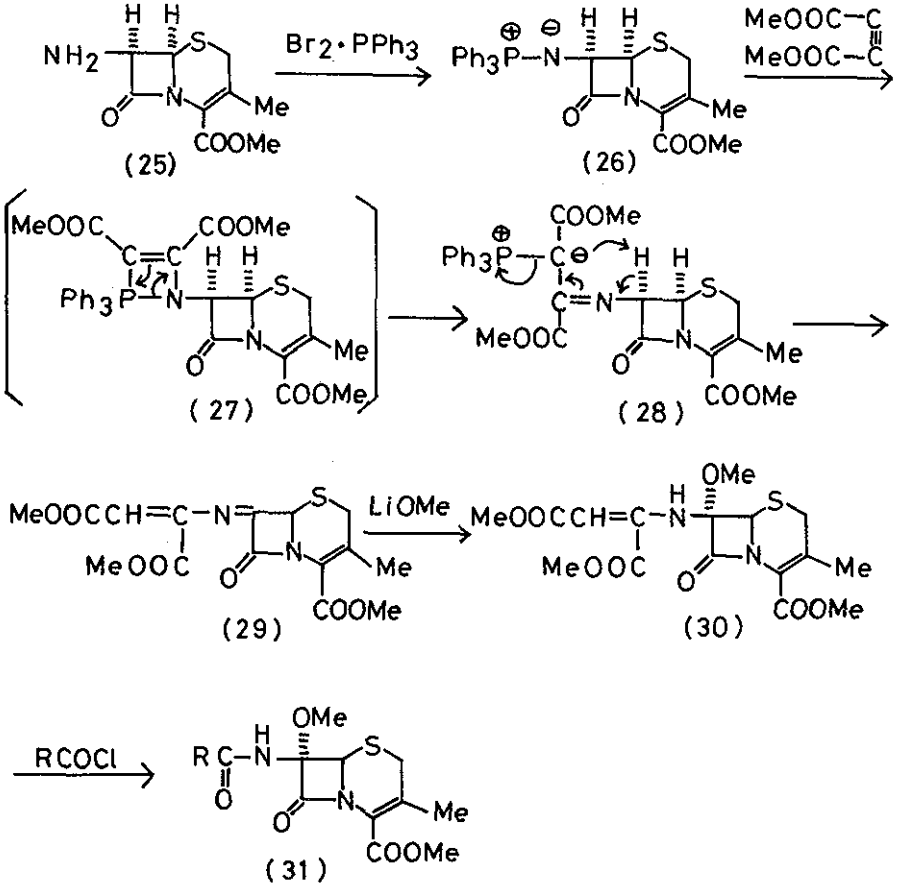


shows that attack of the methoxide anion at the seven position of an intermediate (20) removes the bromine atom located at the ω-position to give the imino chloride (21), which is hydrolyzed to the desired compound (16) during work-up. The formation of the thiazoline (19) is explained by involvement of the nitrilium ion (22). It should be noted that this kind of rearrangement does not occur in 7H-cephalosporins or in a compound having sp^3 carbon with hydrogen(s) at the α to the iminochloride (21) because the hydrogen(s) at such the position would quench the nitrilium


LiOMe
(15)
(16)
(17)
(18)
(19)
(20)
(21)
(22)
(23)
(24)
(i) PCl5
(ii) Br2
(iii) LiOMe - MeOH

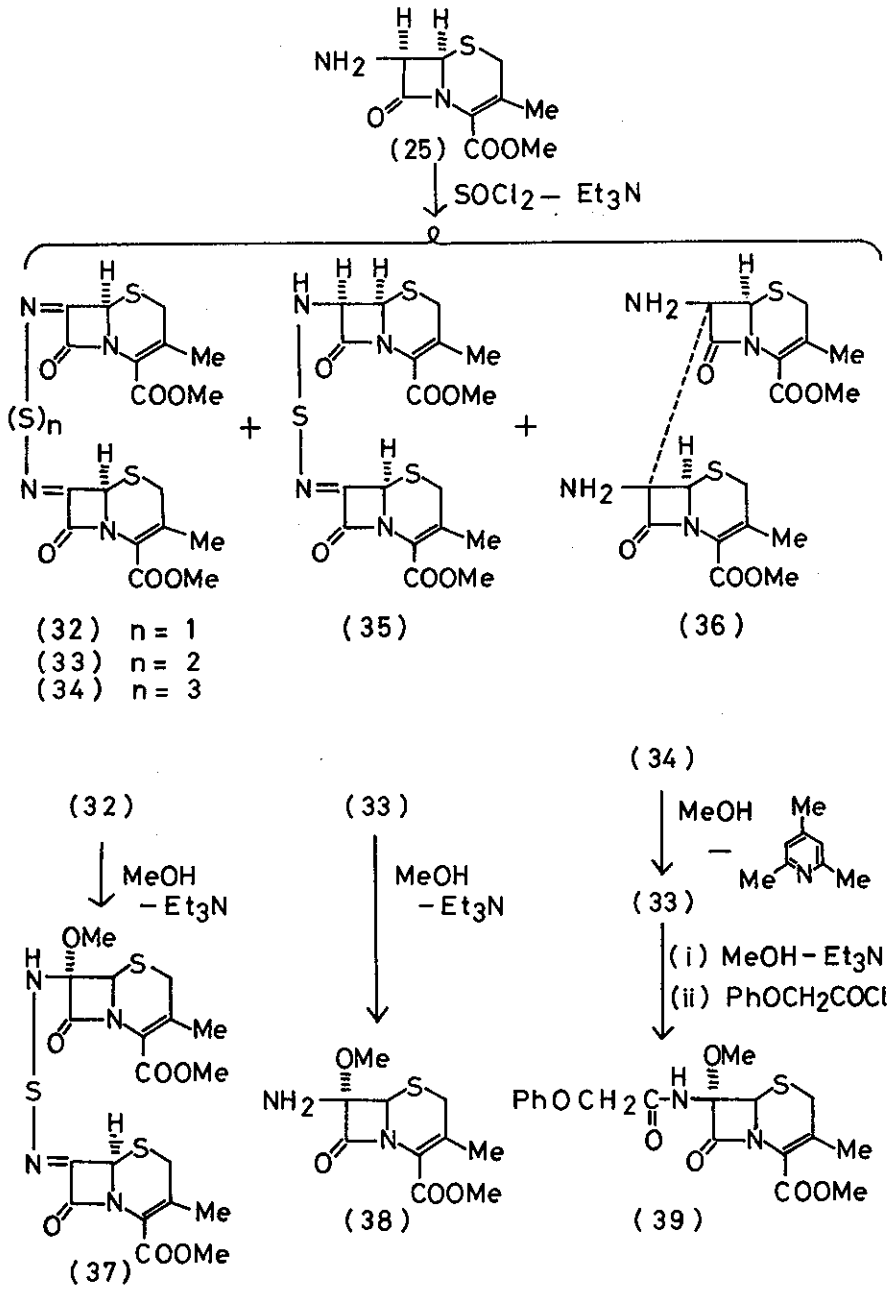
ion (22). The methoxylation reaction described here is practically carried out starting from the unsaturated amide (23) to give the corresponding methoxy derivative (24) on successive treatment with phosphorus pentachloride, bromine and lithium methoxide in methanol.[21]

Next our attention is directed to another type of 1,4-elimination reaction in which elimination species is slightly different.

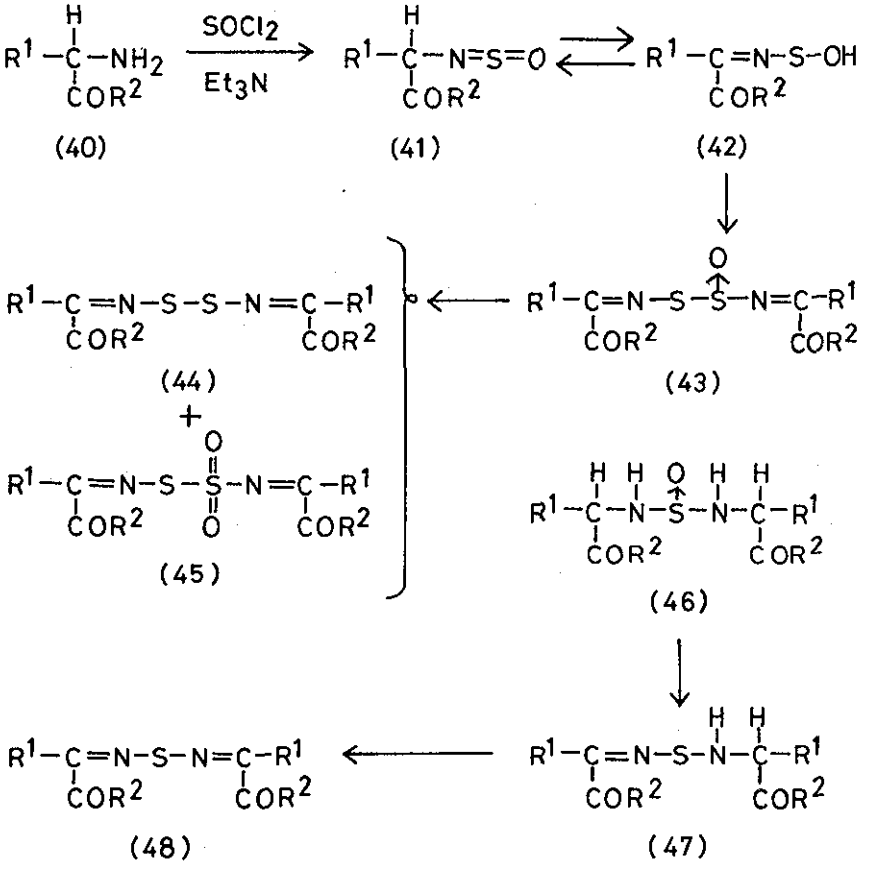


The 7-aminocephalosporin (25) is reacted with triphenylphosphine dibromide according to a usual procedure[22] to furnish P-N-ylide (26) which is treated with dimethylacetylenedicarboxylate as is reported in a phosphorus ylide.[23] As expected the C-P-ylide (28) is obtained together with a small amount of a by-product (29). Examination on the reason for formation of the imine (29) reveals that heating is a driving force for elimination of triphenylphosphine. Thus heating of the ylide (28) in toluene or xylene affords the desired imine (29) through an internal cyclic participation of the ylide carbon in the 7H-hydrogen. The exoimine (29) is easily methoxylated with lithium methoxide in methanol to give the methoxyenamine (30).[24] Some difficulty is encountered in acylation of (30) which has two electron withdrawing groups in the olefinic part resulting in a low basicity of the nitrogen atom. Thus extremely low yield is obtained in the acylation of (30). Although the enamine (30) is very attractive for direct acylation without intervention of rather unstable 7-methoxy-7-amino compound, elaboration of changing substituents or reaction conditions have not been carried out.

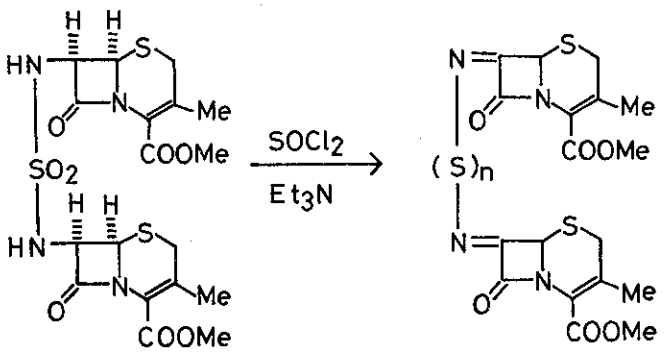
Other methoxylation methods have been further searched in order to establish a versatile method for synthesis of 7α-methoxycephalosporins having complex 7β-acylamino group. Our interests have been centered around sulfur derivatives in which various modification is possible owing to a d-orbital participation. The 7-aminocephalosporin (25) is treated with thionyl chloride in the presence of triethylamine to furnish the symmetrical iminesulfides (32-34), the unsymmetrical sulfide (35) and the


(25)
SOCl2 – Et3N
(32) n = 1
(33) n = 2
(34) n = 3
(35)
(36)
(32)
MeOH
– Et3N
(37)
(33)
MeOH
– Et3N
(38)
(34)
MeOH
(33)
(i) MeOH – Et3N
(ii) PhOCH2COCl
(39)

carbon-carbon dimer (36), after silica gel chromatography.[25] The ratio of the products varies depending on the reaction conditions and the order of the addition of the reagents. In the methoxylation of the sulfides (32) and (33) very curious reactions are observed. Methoxylation of the sulfenimine (32) with methanol in the presence of triethylamine at room temperature produces the monomethoxycephalosporin (37) in good yield. Dimethoxylated product is not obtained even under forced reaction conditions. On the other hand treatment of disulfide (33) with methanol and triethylamine affords 7α-methoxy-7β-aminocephalosporin (38) with extrusion of sulfur moiety. The mechanism of desulfurization or cleavage of S-N bond in this reaction is not clear although *sulfenamides are known to be converted to the corresponding* amines with various nucleophiles.[26] In the cases of trisulfide (34) transformation to the disulfide (33) is observed after treatment with 2,4,6-trimethylpyridine in methanol and dichloromethane at room temperature. A brief discussion of the reaction mechanism for the formation of sulfenimines (32-35) from the primary amine (25) would be helpful for understanding our extensive development following this method. N-Sulfinylamine (41) obtained from the amine (40) would be equilibrated with (42) due to an active hydrogen located at the α-position of the nitrogen atom. The sulfenic acid (42) might be converted to (43), which is disproportionated into the disulfide (44) and thiol sulfonate (45) according to a known sulfenic acid reaction.[27] The reaction of N-sulfinylamine (41) with the starting amine (40) affords the sulfoxide (46), which may be transformed into the unsymmetrical

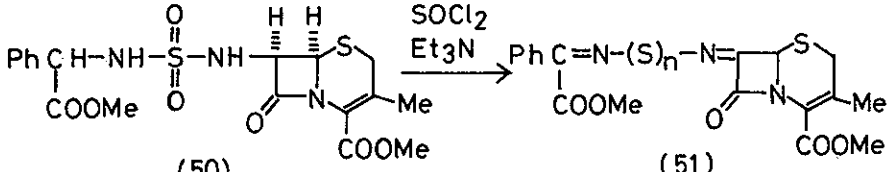


iminosulfide (47) with thionyl chloride. Oxidation of (47) to the symmetrical sulfide (48) would be effected by the reaction with thionyl chloride. This reasoning has been extended to the next reaction. Thus treatment of the sulfamide (49) with thionyl chloride produces the sulfenimine (32) and (34) although yields are not so high.[28] In case of the unsymmetrical sulfamide (50) the desired imine (51) is also obtained. In these reactions a cleavage reaction as depicted in the formula (53) would be operative to furnish sul-



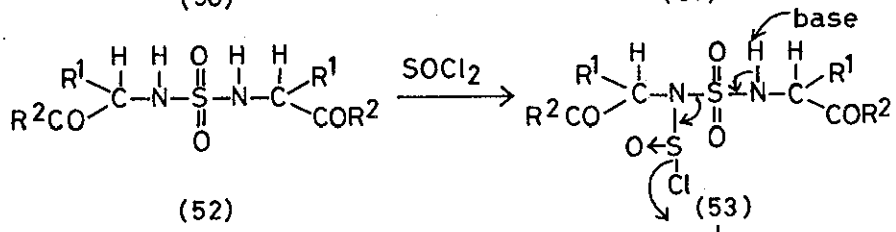
(49)

(32) n = 1
(34) n = 3



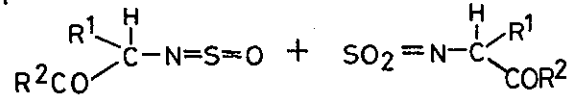
(50)

(51)



(52)

(53)

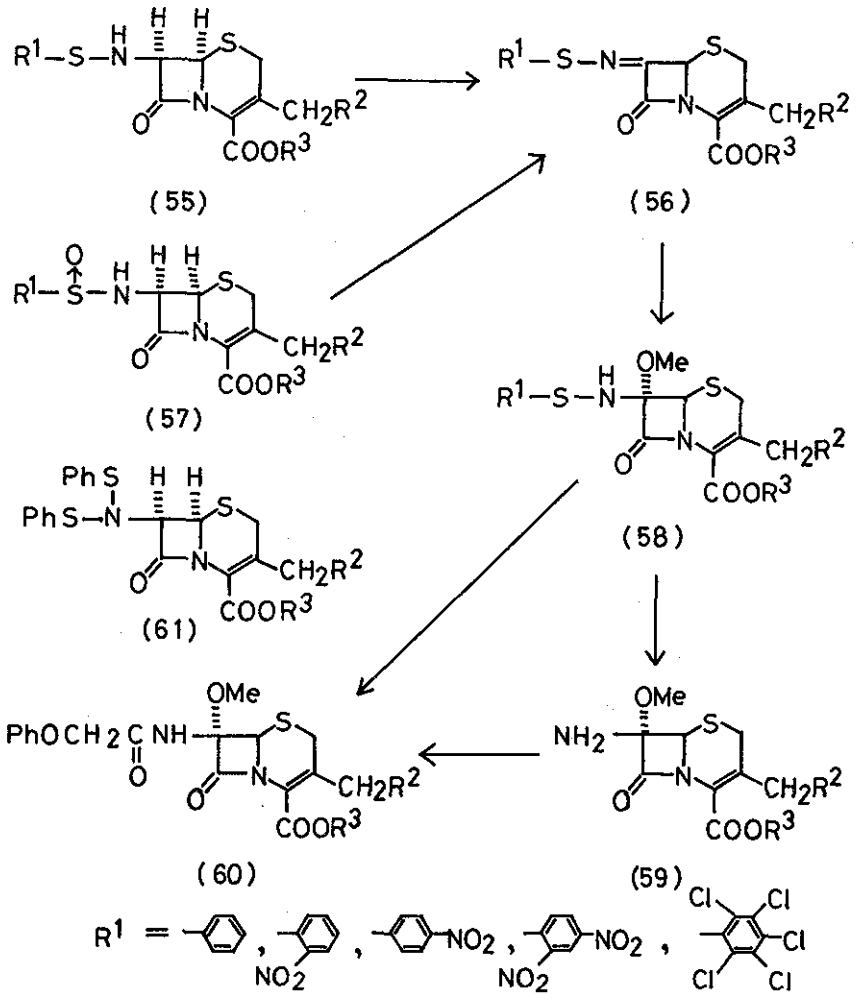


(41)

(54)

finylamine (41) and sulfonylamine (54), both of which might be used leading to the symmetrical sulfide (48) by dimerization mechanism. The detailed possible mechanism is discussed in our paper.[28]

Considering the reactions using thionyl chloride described above a plausible efficient method for methoxylation of cephalosporins at the 7α-position should be a reaction starting from the sulfenamide (55), which is easily obtained from substituted sulfenyl chloride and 7-aminocephalosporins. An alternative starting material should be the sulfinylamino derivative (57). The efficiency of the thiooxime (56) as an intermediate is verified by the fact that the imine (56) is already produced during the synthesis of the sulfenamide (55) by the reaction of a 7-aminocephalosporin and benzenesulfenyl chloride as a minor product together with disulfenylamino compound (61).[29] Oxidation reaction or N-halogenation-dehydrohalogenation of the sulfenylamino derivative (55) has been extensively studied. Manganese dioxide is found to be the most effective for the present purpose. Other oxidative reagents such as trichloroisocyanuric acid, NCS or t-butyl hypochlorite with triethylamine are less satisfactory than MnO_2. The thiooxime (56) was also obtained from the sulfinylamino derivative (57) on treatment with thionyl chloride in the presence of quinoline as easily expected in the former reactions. Methoxylation of the imine (56) is smoothly conducted by the reaction with lithium methoxide in methanol or methanol with t-butoxide as a catalyst when the benzene ring of R^1 possesses electron withdrawing group(s). Thus mono or dinitrophenyl or

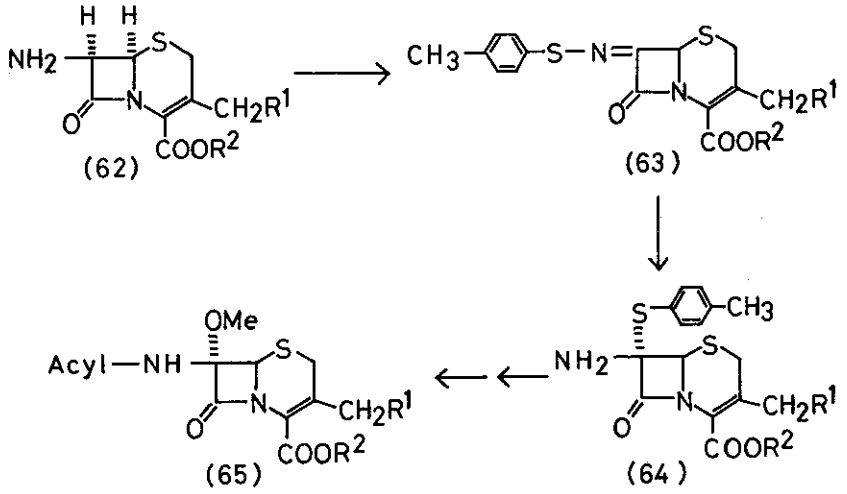


pentachlorophenyl derivatives (56) are methoxylated at -78° to furnish the 7α-methoxysulfenamides (58) stereospecifically in good yields, while phenylsulfenylamino derivatives (56) (R^1=Ph) affords a trace of the methoxy compound (58) with methoxide anion. Interestingly, methoxylation with an acid catalyst such as methanesul-

fonic acid or p-toleunesulfonic acid at room temperature gives a mixture of 7α- and 7β-methoxy derivatives.[29] The methoxysulfenamide compound (58) is an attractive intermediate for acylation since a sulfenamide group can be converted to an amide by reaction with a carboxylic acid.[30] Application of this coupling method[30] for peptide formation to the methoxysulfenamide (58) is unsatisfactory. This is not unusual based on the observation that there is a great difference in reactivity between 7α-H-7β-aminocephalosporins and the 7α-methoxy-7β-amino series. For example, the 7α-H-sulfenamide (55) is reacted with phenoxyacetyl chloride without a base to give the corresponding 7β-phenoxyacetamide in excellent yield, whereas the same reaction starting from the 7α-methoxysulfenamide (58) affords acylated product (60) in poor yield (about 5%). This difference would be due to a steric hindrance and lower basicity of the nitrogen atom of the 7α-methoxy-7β-sulfenylamino group. The sulfenylamino moiety of the derivative (58) is removed with sodium iodide or thiophenol or hexamethylphosphorus triamide to furnish the free amine derivative (59), which is a versatile starting material for preparation of various active cephamycin derivatives.

Recently, at Squibb institute Gordon et al. develops a similar new reaction which starts from the free amine (62) to give the thiooxime (63) in a single step on treatment with toluenesulfenyl chloride.[31] The imine (63) rearranges into (64) by reaction with triphenylphosphine in high yield. The tolylthio group is easily substituted by methoxide with mercuric ion after acylation of the primary amine (64) to afford the desired 7α-

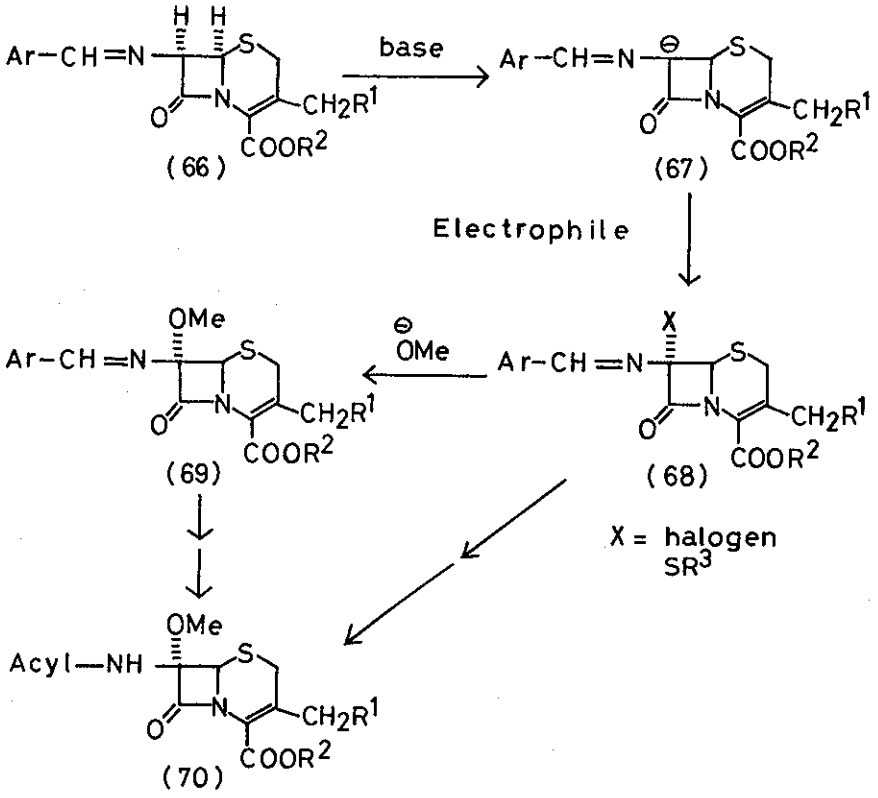
methoxy-7β-acylaminocephalosporins (65).



III. Syntheses of 7α-methoxycephalosporins through a 7-anion system

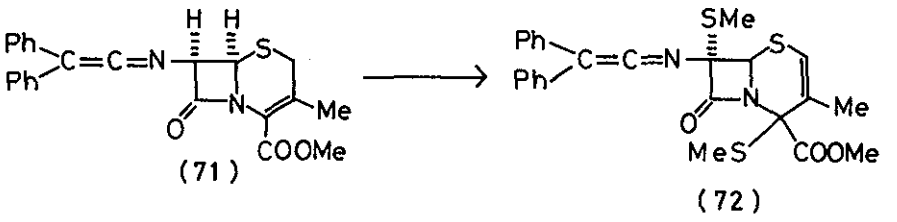
Another method for 7-methoxylation of cephalosporins comprises the formation of the 7-anion (67) as an intermediate, which is treated with an electrophile such as a halogenating reagent or a potential thio-cation to give the compound (68) having a halogen or thio group at the seven position. This kind of reaction stems from an older substitution reaction by a carbon compound at the same position.[32] A number of groups have reported these reactions to obtain various cephamycin derivatives (70) with slightly modified methods.[33]

We have also tried this kind of reaction starting from 7H-ketenimine (71) to give the 7-methylthio derivative (72) on suc-



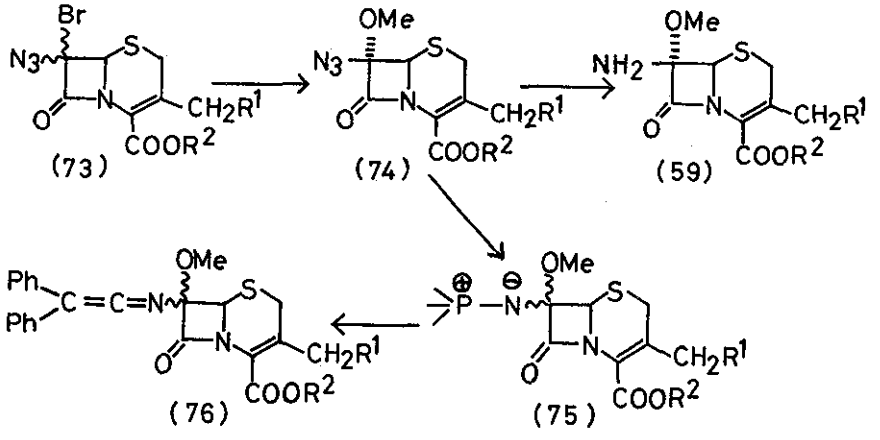
cessive treatment with n-butyllithium and $CH_3SSO_2CH_3$, however, the results are not so satisfactory due to a preferential formation of a 2-cephem derivative.[34] This method is an indirect methoxylation and some problems seem to be present from industrial point of view.

In this classification, earlier Merck's method should be briefly mentioned. Bromoazide derivative (73) obtained from a diazonium compound by treatment with bromine azide is converted to 7α-methoxy-7β-amino cephalosporin (59) by methoxylation and



(71) (72)

hydrogenation.[35] In our earlier investigation we have tried to confirm our methoxylated ketenimine product (8). Thus Merck's intermediate (74) (R^1=H, R^2=CH_3) is converted to P-N ylide (75) on treatment with triphenylphosphine, and successive reaction with diphenylketene affords 7-methoxy-7-diphenylketene (76) in low yield. Surprisingly the product (76) obtained here is not identical with one obtained by the reaction starting from (6). Examination of the spectroscopic data reveals that the product (76) derived through the Merck's intermediate is an isomer, namely, 7β-methoxy-7α-diphenylketenimine.[36] This result can be explained by the following reasoning. The reaction of the methoxy-



(73) (74) (59) (76) (75)

azide (74) with bulky triphenylphosphine takes place only in the 7β-methoxy-7α-azide derivative contained in the compound (74) as a minor product due to a shorter reaction time to give 7β-methoxy-7α-iminophosphorane (75), which is transformed to 7β-methoxy-7α-ketenimine (76). The low yield from (74) to (76) also supports this inference.

IV. Conclusion

Various methods for 7α-methoxylation of cephalosporins have been developed by many groups as reviewed in this article. The one selected method has merits with other kind of demerits depending upon the nature of the 7β-acyl-moiety. Therefore the choice of the method should be determined on the basis of the structure of a desired product. Generally speaking, if the target 7α-methoxy compound has a complex polyfunctionalized 7β-acyl group *7α-methoxy-7β-amino derivative is a suitable starting material*, whereas in the case of simple 7β-acyl moiety other kinds of choice are present.

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