SYNTHESIS OF GEOMETRICAL ISOMERS OF 3-(3-ACETOXY AND 3-CARBAMOYLOXY-1-PROPENYL)-CEPHALOSPORINS AND THEIR STRUCTURE-ACTIVITY RELATIONSHIPS

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In the course of our research program exploring new cephalosporins, we have found that 3-[(*Z*)-1-propenyl] derivatives, such as BMY-28100 (cefprozil)[1] and BMY-28232[2], showed Gram-negative activity superior to their corresponding 3-(*E*)-propenyl isomers, whereas 3-[(*E*)-3-quaternary-ammonio-1-propenyl]cephalosporins[3] were more active than their corresponding *Z*-isomers against both Gram-positive and Gram-negative bacteria. BEEBY and EDWARDS[4] reported the synthesis of *E*-isomer of 7-(2-thienylacetamido)-3-(3-acetoxy-1-propenyl)cephalosporin and its potent antibacterial activity, but did not describe on its *Z*-isomer. It is of interest to clarify the structure-activity relationships between the geometrical isomers of cephalosporins having a 3-acetoxy- or 3-carbamoyloxy-1-propenyl group at the C-3 position. Here we wish to report on the synthesis of three pairs of geometrical isomers of the above cephalosporins, **1**~**6** (Fig. 1), using the Wittig reaction for the introduction of the *Z*-propenyl groups and rearrangement of them to the *E*-propenyl groups. The structure-activity relationships between the geometrical isomers is described.

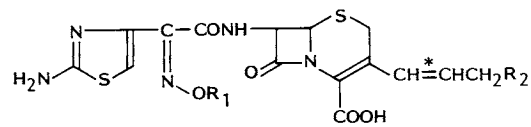
Synthesis of Cephalosporins **1** and **2** (Scheme 1)

3-[(*E*)-3-Carbamoyloxy-1-propenyl]cephalosporin (**1**) was synthesized from [(*Z*)-3-chloro-1-propenyl]cephem ester (**7**)[3]. It was treated with $AgNO_3$[5] in aqueous DMSO (4 hours at room temperature) to give **8** (65%; ^{1}H NMR ($CDCl_3$) δ 6.93 (1H, d, J=16 Hz, 3-C*H*=CH)). Compound **8** was treated with trichloroacetylisocyanate[6], followed by successive treatment with TFA and 2 N Na_2CO_3, to give **1** (13%; ^{1}H NMR (DMSO-d_6) δ 6.96 (1H, d, J=16 Hz, 3-C*H*=CH)). 3-[(*Z*)-3-Carbamoyloxy-1-propenyl]cephalosporin (**2**) was synthesized by direct introduction of the (*Z*)-carbamoyloxypropenyl group to the C-3 side chain by the Wittig reaction. As 2-carbamoyloxyacetaldehyde was unstable[7], *N*-trityl-protected 2-carbamoyloxyacetaldehyde (**10**) was employed. Tritylamine was treated with allyl chloroformate in the presence of bis(trimethylsilyl)acetamide (2 equiv) in CH_2Cl_2 (room temperature, overnight) to give allyl *N*-trityl carbamate (**9**) (91%; mp 97~98°C), which was subjected to ozonolysis in CH_2Cl_2 at −78°C and subsequent treatment with dimethyl sulfide to give the aldehyde **10** (71%; mp 93~96°C). The ylide **11** was conventionally prepared[1,2] by treatment of 7-*N*-Boc-3-chloromethylcephem ester with triphenylphosphine in CH_2Cl_2 followed by treatment with 5 N Na_2CO_3. The Wittig reaction of **11** and the aldehyde **10** in CH_2Cl_2 (room temperature, 3 days), afforded 3-[(*Z*)-3-carbamoyloxy-1-propenyl]-cephem **12** (42%; ^{1}H NMR (DMSO-d_6) δ 6.23 (1H, d, J=12 Hz, 3-C*H*=CH)). Deblocking of **12** with HCO_2H-HCl (2:1, 1 hour, room temperature), gave **13** (66%; ^{1}H NMR (D_2O+$NaHCO_3$) δ 6.22 (1H, d, J=12 Hz, 3-C*H*=CH)). Acylation of **13** with benzotriazol-1-yl (*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate[8] in DMF in the presence of $NaHCO_3$ afforded **2** (34%; ^{1}H NMR (DMSO-d_6) δ 6.36 (1H, d, J=12 Hz, 3-C*H*=CH)).

Synthesis of Cephalosporins **3**~**6** (Scheme 2)

Synthesis of 3-[(*Z*)-3-acetoxy-1-propenyl]cephalosporins (**4** and **6**) was by way of the 7-*N*-

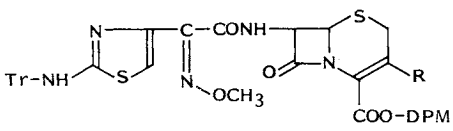
Fig. 1. 3-[(*E*)- and (*Z*)-3-substituted-oxy-1-propen-1-yl]cephalosporins.



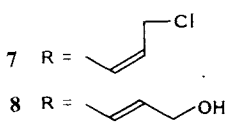
Compound	R_1	R_2	*
1	CH_3	$OCONH_2$	*E*
2	CH_3	$OCONH_2$	*Z*
3	CH_3	$OCOCH_3$	*E*
4	CH_3	$OCOCH_3$	*Z*
5	H	$OCOCH_3$	*E*
6	H	$OCOCH_3$	*Z*

† Deceased.

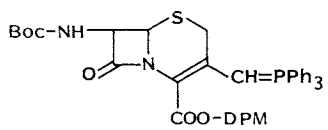
Scheme 1. Synthesis of 3-carbamoyloxypropenylcephalosporins.



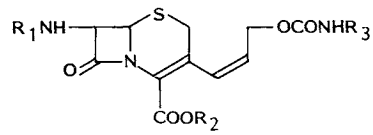
Tr-NHR



9 R = $COOCH_2CH=CH_2$
10 R = $COOCH_2CHO$



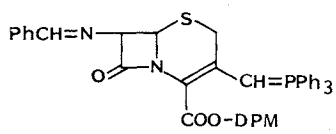
11



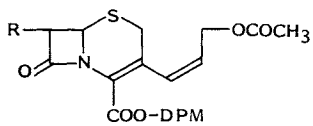
12 R_1 = Boc R_2 = DPM R_3 = Tr
13 $R_1 = R_2 = R_3 = H$

Tr = CPh_3, DPM = $CHPh_2$

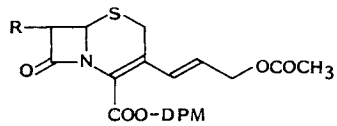
Scheme 2. Synthesis of 3-acetoxypropenylcephalosporins.



14



15 R = PhCH=N–
16 R = H_2N–
17 R = BocNH–



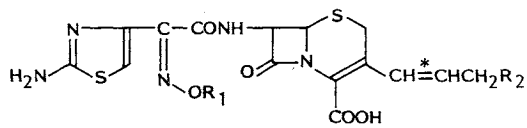
18 R = BocNH–
19 R = H_2N–

benzylidene-cephem-3-ylide **14**[2]. The Wittig reaction of **14** with acetoxyacetaldehyde[9] in the presence of excess LiBr (10 equiv) in DMF-CH_2Cl_2 (room temperature, overnight) gave the 3-(*Z*)-acetoxypropenyl-7-*N*-benzylidene-cephem (**15**). The benzylidene group of **15** was deblocked with the Girard T reagent to give the 7-aminocephem (**16**) (68% after crystallization from ether; mp 117~119°C; ^{1}H NMR ($CDCl_3$) δ 6.25 (1H, d, J=12 Hz, 3-C*H*=CH)). Compound **16** was acylated with benzotriazol-1-yl (*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate and (*Z*)-2-(2-tritylaminothiazol-4-yl)-2-trityloxyiminoacetate[2] (THF, 18 hours, room temperature) and deblocked with HCO_2H-HCl[2] to give **4** (37%; ^{1}H NMR (DMSO-d_6) δ 6.34 (1H, d, J=12 Hz, 3-C*H*=CH)) and **6** (36%; ^{1}H NMR (DMSO-d_6) δ 6.35 (1H, d, J=12 Hz, 3-C*H*=CH)). In order to obtain the corresponding *E*-isomers, **3** and **5**, thermal isomerization of the propenyl group of **17** was attempted. The Wittig reaction of **11** with acetoxyacetaldehyde gave *Z*-(3-acetoxy-1-propenyl)cephem **17**, which was dissolved in toluene and heated under reflux for 2 days to afford *E*-(3-acetoxy-1-propenyl)cephem, **18** (51% after crystallization from ether; mp 161~163°C (dec); ^{1}H NMR ($CDCl_3$) δ 6.90 (1H, d,

Table 1. Test organisms.

Group	Organism	Number of strains
Gp-Ia	Penicillinase (Pen-ase)-negative *Staphylococcus aureus*	5
Gp-Ib	Pen-ase-positive *S. aureus*	5
Gn-Ia	Cephalothin(CET)-sensitive *Escherichia coli* (2 strains), *Klebsiella pneumoniae* (1) and *Proteus mirabilis* (2)	5
Gn-Ib	CET-resistant *E. coli* (3) and *K. pneumoniae*	5
Gn-II	*Morganella morganii* (1), *Enterobacter cloacae* (2) and *Serratia marcescens* (2)	5
Gn-III	*Pseudomonas aeruginosa*	7

Table 2. *In vitro* activity of the geometrical isomers of cephalosporins (Mueller-Hinton agar, 10^6 cfu/ml, 37°C, 18 hours).



Compound	R_1	R_2	*	Geometric mean of MIC (μg/ml)					
				Gp-Ia	Gp-Ib	Gn-Ia	Gn-Ib	Gn-II	Gn-III
1	CH_3	$OCONH_2$	*E*	1.1	1.8	0.044	0.17	0.91	>50
2	CH_3	$OCONH_2$	*Z*	0.92	1.6	0.0082	0.087	0.79	28
3	CH_3	$OCOCH_3$	*E*	0.53	0.80	0.019	0.087	0.53	>50
4	CH_3	$OCOCH_3$	*Z*	0.61	1.6	0.025	0.13	0.80	>50
5	H	$OCOCH_3$	*E*	0.17	0.40	0.025	0.17	1.2	>50
6	H	$OCOCH_3$	*Z*	0.30	0.40	0.029	0.11	0.91	>50
20	H	H	*E*	0.23	0.61	0.46	2.1	33	>50
21	H	H	*Z*	0.23	0.40	0.076	0.35	5.5	>50
22	H	CH_3	*E*	0.23	0.61	0.69	3.2	22	>50
23	H	CH_3	*Z*	0.26	0.40	0.20	0.79	7.3	>50
24	CH_3	$N^+(CH_3)_3$	*E*	0.23	0.80	0.011	0.076	0.087	2.4
25	CH_3	$N^+(CH_3)_3$	*Z*	0.61	1.4	0.029	0.11	0.20	3.8
26	CH_3		*E*	0.15	0.35	0.0094	0.038	0.057	1.7
27	CH_3		*Z*	0.35	0.80	0.029	0.087	0.15	3.8
Cefotaxime				1.2	2.7	0.025	0.087	1.2	21

$J=16$ Hz, 3-C*H*=CH)). Selective deblocking of **18** by treatment with *p*-toluenesulfonic acid (2 equiv) in acetonitrile (40°C, 40 minutes) gave 7-aminocephem **19** (84%; ^{1}H NMR ($CDCl_3$) δ 6.90 (1H, d, $J=16$ Hz, 3-C*H*=CH)). *N*-Acylation of **19** with the active esters followed by deblocking gave the *E*-isomers **3** (46%; ^{1}H NMR (DMSO-d_6) δ 6.85 (1H, d, $J=16$ Hz, 3-C*H*=CH)) and **5** (51%; ^{1}H NMR (DMSO-d_6) δ 6.87 (1H, d, $J=16$ Hz, 3-C*H*=CH)).

Structure-activity Relationships between The Geometrical Isomers

MICs of the cephalosporins **1** through **6**, together with two pairs of the geometrical isomers of 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-(1-alkenyl)cephalosporins[2], **20** through **23**, and the two pairs of 7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(3-quaternary ammonio-1-propenyl)cephalosporins[3], **24** through **27**, were determined by two-fold serial agar dilution method in Mueller-Hinton agar. The test organisms consisted of six groups which are described in Table 1. The *in vitro* activity of the derivatives was assessed by the geometric means of MICs for each group of the test organisms and summarized in Table 2. As we already

reported[2,3], in the 3-(1-alkenyl)cephalosporins, which showed good Gp, rather weak Gn-Ib, weak Gn-II and very weak Gn-III activity, the *Z*-isomers, **21** and **23**, were as active as the corresponding *E*-isomers, **20** and **22**, against Gp-Ia and Gp-Ib, respectively, but they were much more active against Gn-Ia, Gn-Ib and Gn-II than the corresponding *E*-isomers. In contrast, in the cephalosporins having a quaternary ammonio group in 3-position of the propenyl group and showing high and broad anti-bacterial spectrum including good Gn-III activity, the *E*-isomers, **24** and **26** were more active than the corresponding *Z*-isomers, **25** and **27** against all groups of the strains. The cephalosporins synthesized in this study showed higher Gn-Ib and Gn-II activity than the 3-(1-alkenyl)cephalosporins with very weak Gn-III activity. Among them, the *Z*-isomer of 3-carbamoyloxypropenyl derivative, **2**, was much more active against Gn-Ia and slightly more active against the other groups of strains than the *E*-isomer **1**, while, in the 3-acetoxypropenyl derivatives, there were no significant differences between the activity of the *E*-isomers and their corresponding *Z*-isomers, although **3** (*E*-isomer) is slightly more active than **4** (*Z*-isomer) against all of the groups. In conclusion, the Gram-negative activity of 7-aminothiazol-oxyiminoacetyl-cephalosporins having 3-(3-substituted-1-propenyl) group as well as the structure-activity relationships between their geometrical isomers depends on the substituent introduced into the 3-position of the propenyl group.

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