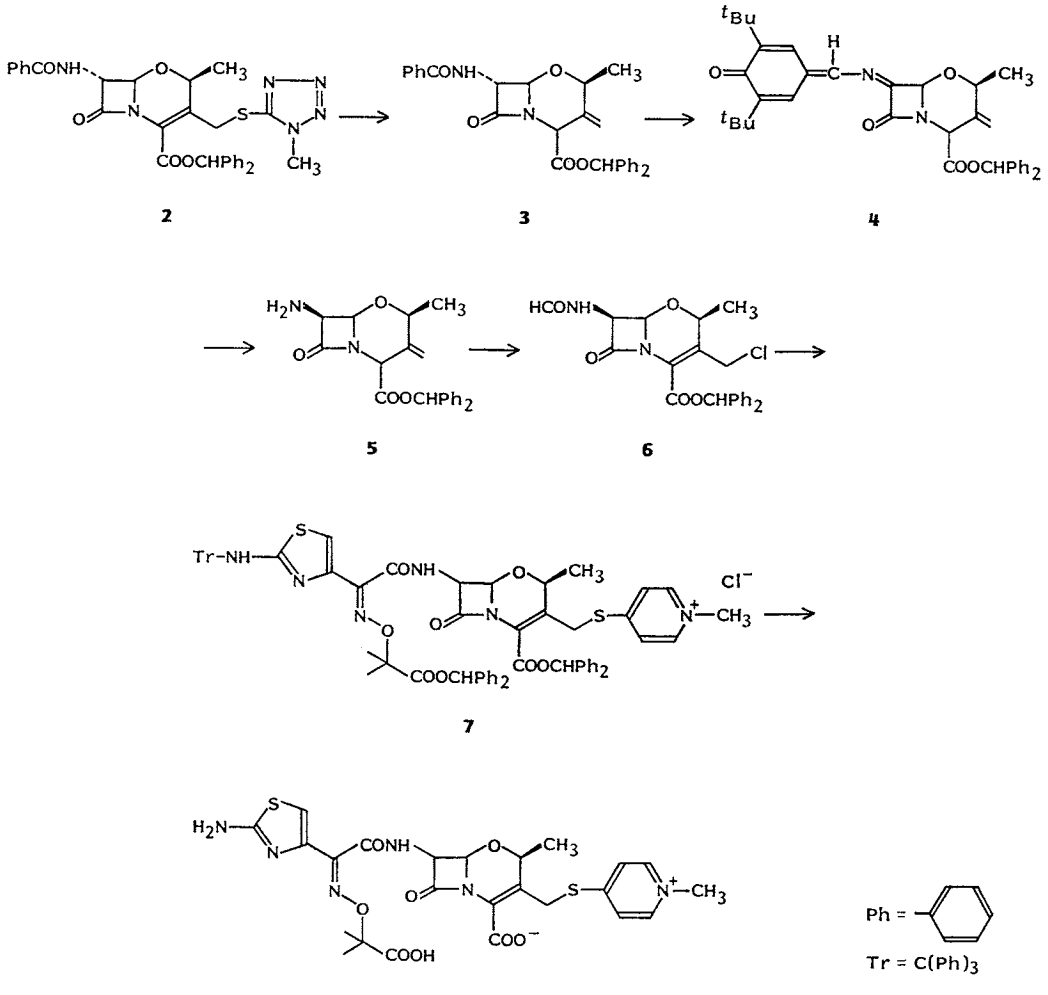
SYNTHESIS OF A NOVEL 2β-METHYL-1-OXACEPHALOSPORIN, OCP-9-176†

Sir:

As reported in our previous report[1] 7α-benzoylamino-2-methyl-1-oxacephems were synthesized from 6-APA through (3*R*,4*S*) phenyloxazolinoazetidinone.[2,3] We synthesized the 2α-methyl and 2β-methyl isomers stereoselectively, with variation of the C-3 side chains.[4,5] We wish to report herein the synthesis of a novel 2β-methyl-1-oxacephalosporin, OCP-9-176 (**1**) and its related compounds from **2**:[4] 7α-benzoylamino-2β-methyl-3-(*N*-methyl)tetrazoylthiomethyloxacephem. Compound **1** shows a potent antibacterial activity.

Compound **2** was reduced with zinc powder[6] in the presence of ammonium chloride and thiourea in DMF to give exomethylene compound **3** (95%, yield). Debenzoylation of **3** with PCl_5 and MeOH,[7] and Schiff base formation of the resulting α-amino group with 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde[8] followed by oxidation with nickel peroxide[9] afforded quinomethine intermediate **4**. Stereoselective reduction of **4**

Scheme 1.



† Presented in part at the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, Oct. 4~7, 1987.[1]
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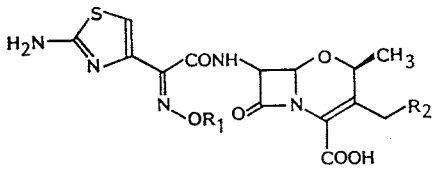
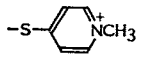
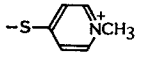
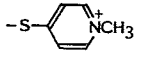
Table 1. MICs (μg/ml).[a]



Compound	R_1	R_2	S.a-1[b]	S.a-2	E.c-1[b]	E.c-2	E.c-3[c]	K.p	P.v	M.m[c]	C.f[c]	P.a-1[c]	P.a-2
OCP-9-176 (**1**)	$C(CH_3)_2COOH$		3.13	0.78	0.39	0.20	0.39	0.20	0.10	0.39	0.78	1.56	0.78
8	CH_3		0.20	0.10	0.20	0.05	0.20	0.05	0.39	0.39	1.56	12.5	6.25
9	CH_2COOH		1.56	0.78	0.20	0.025	0.39	0.05	0.05	0.20	3.13	1.56	1.56
10	$C(CH_3)_2COOH$		12.5	6.25	0.78	0.20	12.5	0.39	0.20	6.25	12.5	12.5	12.5
Ceftazidime			6.25	3.13	0.20	0.20	12.5	0.20	0.05	12.5	50	1.56	0.78

[a] MICs were determined by a 2-fold dilution in Mueller-Hinton agar; inoculum of 10^6 cfu.

[b] Penicillinase producer.

[c] Cephalosporinase producer.

Organisms abbreviations: S.a-1, *Staphylococcus aureus* 606; S.a-2, *S. aureus* Smith; E.c-1, *Escherichia coli* W3630 RGN14; E.c-2, *E. coli* NIHJ JC-2; E.c-3, *E. coli* 255; K.p, *Klebsiella pneumoniae* PCI 602; P.v, *Proteus vulgaris* GN76; M.m, *Morganella morganii* 1510; C.f, *Citrobacter freundii* GN346; P.a-1, *Pseudomonas aeruginosa* M-0148; P.a-2, *P. aeruginosa* IAM 1007.

with tetraethylammonium borohydride followed by treatment with Girard T reagent gave 7β-amino compound **5** in 35% yield from **3**. After the amino group of **5** was protected by a formyl group with *O*-formyl-2,4,5-trichlorophenol (79%, yield), the resulting formamide was reacted with phenylselenyl chloride,[10] followed by oxidation with peracetic acid to give a versatile intermediate, 2β-methyl-3-chloromethyl-1-oxacephem **6** in 52% yield. Deformylation of **6** with HCl, acylation of the resulting 7β-amino compound with 2-(2-tritylaminothiazol-4-yl)-2-(1-diphenylmethoxycarbonyl - 1 - methylethoxy)iminoacetic acid[11] by using $POCl_3$ and pyridine,[12] and followed by the successive treatment with 1-methyl-4(1*H*)-pyridinethione[13] in DMF afforded **7** in 85% yield. Compound **7** was deprotected with TFA and anisole, and the crude antibiotic was purified with a column of Diaion HP-20 to give **1** in 65% yield.

Compound **1** was isolated as the sodium salt in an amorphous powder: MP 175~180°C (dec); $[\alpha]_D^{25}$ −48.7° (*c* 1.88, H_2O); NMR (D_2O) δ 1.45 (3H, s), 1.47 (3H, s), 1.49 (3H, d, J=7.0 Hz), 3.80 and 4.80 (2H, ABq, J=17 Hz), 4.19 (3H, s), 4.73 (1H, q, J=7.0 Hz), 5.17 (1H, d, J=3.5 Hz), 5.58 (1H, d, J=3.5 Hz), 7.00 (1H, s), 7.70 and 8.40 (4H, ABq, J=6.2 Hz); IR(KBr) cm^{-1} 3340, 1775, 1730, 1650.

Alkoxime homologs (**8** and **9**) of **1** and the pyridiniummethyl derivative (**10**) at C-3 were similarly prepared from the deformylated derivative of **6**. Their *in vitro* antibacterial activities are shown in Table 1. Methoxime compound showed broad spectrum against Gram-positive and Gram-negative bacteria but the activity against *Pseudomonas aeruginosa* was lower than that of ceftazidime. The introduction of carboxylic group in the alkoxime moiety (**1** and **9**) clearly increased the anti-pseudomonal activity. Among compounds **1**, **8** and **9**, *gem*-dimethylcarboxymethoxime compound **1** showed the best anti-pseudomonal activity which is comparable to that of ceftazidime. Interestingly, the 2β-methyl-1-oxa counterpart (**10**) of ceftazidime was inferior to ceftazidime and **1**. Compound **1** is more active than ceftazidime against *Staphylococcus* strains and β-lactamase-producing Gram-negative bacteria. It is noteworthy that the 2β-methyloxacephalosporins possess high antibacterial activity, while 2-non-methyloxacephalosporin aminothiazole congeners[14] have unremarkable activity. Namely 2-non-methyl analog of OCP-9-176, prepared in our laboratory showed low degree of the activity against cephalosporinase producing Gram-negative bacteria: *Escherichia coli* 255 (MIC 6.25 μg/ml), *Morganella morganii* 1510 (3.13 μg/ml) and *Citrobacter freundii* GN346 (50 μg/ml). Thus, we demonstrated that the introduction of 2β-methyl group on 1-oxacephems not only increased the intrinsic activity, but the activity against β-lactamase producing strains as well. In conclusion, OCP-9-176 (**1**) having a well-balanced spectrum and β-lactamase stability was selected for further evaluations.[15,16] The structure-activity relationships of 2-methyl-1-oxacephalosporins will be reported in details elsewhere.

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