2α-ALKOXYMETHYL CEPHALOSPORINS: REACTIONS OF *exo*-2-METHYLENE CEPHALOSPORIN SULFONES WITH ALCOHOLS

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A series of 2α-alkoxymethyl cephem sulfones were prepared by nucleophilic addition of a variety of alcohols to *exo*-2-methylene cephem sulfones. The 2α-alkoxymethyl group was introduced with the aim of improving the inhibitory activity against human leukocyte elastase (HLE) over the unsubstituted compounds. However, against HLE the in vitro activity was still inferior to that shown by the C-2 unsubstituted cephem sulfones.

In recent years much attention has focused on the chemical modification of the C-2, C-3, C-4 and C-7 position of the cephalosporin moiety with the aim of obtaining potent elastase inhibitors[1–4]. Some of these inhibitors also show in vivo activity such as *I* and *II* which prevent lung damage in hamsters treated intratracheally with human leukocyte elastase[1,5] (HLE).

Our effort in this area has produced a series of 2-spirocyclopropyl cephem sulfones (*III*) with the derivatization of the carboxylic function at the C-4 position of the cephem nucleus as esters[6], amides[7], and ketones[8] and were found to exhibit potent inhibitory activity against HLE. It is further evidenced from the subsequent literatures[9] that the introduction of a substituent at C-2 position of the cephem skeleton will generally increase inhibitory activity against HLE; examples of such inhibitors include 2α- and 2β-CH_3, 2α-OCH_3, and 2α-CH_2SPh. Alpegiani et al.[2,3] further reported a series of C-2 substituted cephem-4-ketones (*IV*) as potent elastase inhibitors. On these grounds, a research programme devoted to the synthesis and evaluation of new C-2 substituted cephem sulfones was undertaken in our laboratory. We wish to report here the synthesis of 2α-alkoxymethyl cephem sulfones *V*.

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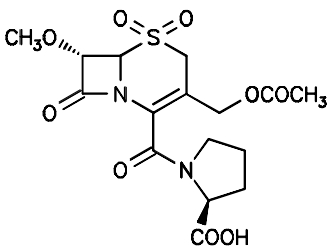
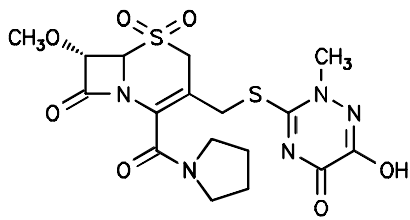
In 1971, Wright et al.[10] reported that refluxing of cephalosporin sulfoxide esters in a mixture of 2-methyl-2-propanol and methylene chloride with aqueous formaldehyde under Mannich conditions gave a single product, *exo*-2-methylene sulfoxide. In an attempt to introduce a double bond at C-2 position of the cephem sulfone *VI* under such conditions we found that the cephem sulfone *VIa*, gave *exo*-2-methylene cephem sulfone *VIIIa* as the major product, along with a minor product *Va* (Scheme 1). This interesting observation prompted us to investigate the reaction in detail. Suprisingly, when methylene chloride was replaced with dioxane, no alkoxymethyl cephem derivative *Va* was observed.

The intermediate *VIIa* under the reaction conditions can undergo nucleophilic displacement by 2-methyl-2-propanol or the product *VIIIa* can undergo nucleophilic addition at the exocyclic double bond to form the 2α-alkoxymethyl cephem sulfone *Va*. This is readily proven by the fact that the *exo*-2-methylene cephem sulfones *VIII* can be converted to *V* by further reaction with a variety of alcohols like methanol, ethanol, 2-propanol and 2-methyl-2-propanol at ambient to refluxing temperatures using methylene chloride as a solvent. The isolated products *V* were not a mixture of C-2 epimers, but they were single compounds (2α-isomer) in each case. The stereoselectivity of additions to the exocyclic double bond has been described elsewhere[9]. The nature of the ester protecting group R^4 affected the ease of the addition. With electron withdrawing trichloroethyl group, the addition was much faster but with electron donating



I



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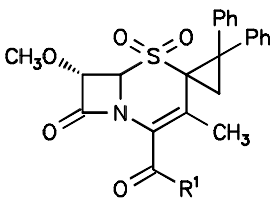
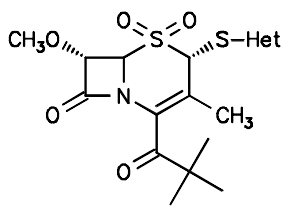
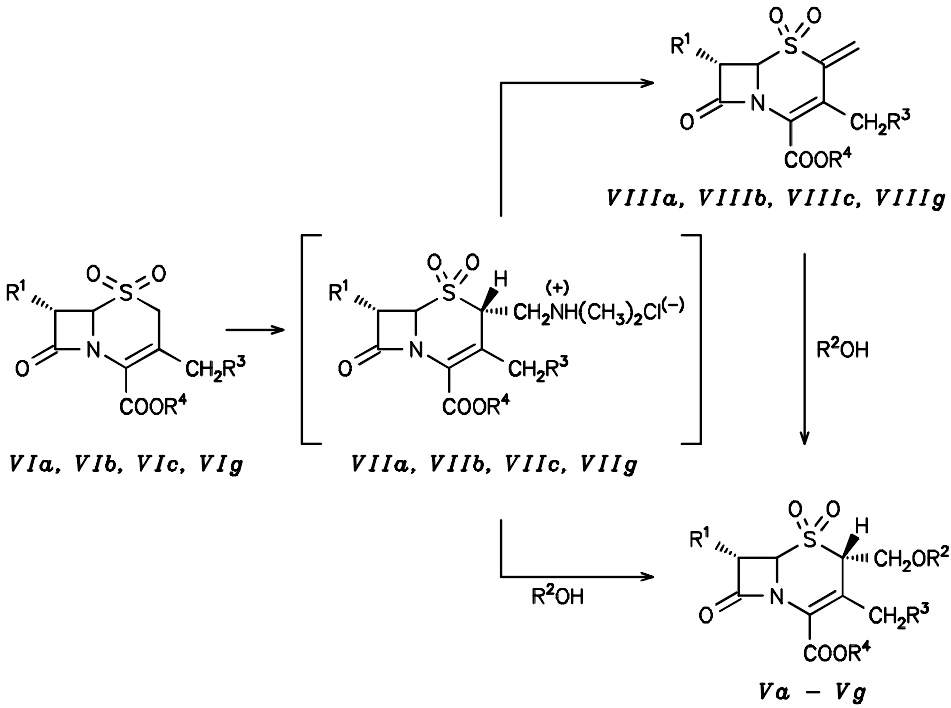


III



IV

tert-butyl esters no addition was observed even with methanol. As would be expected both from steric and nucleophilic effects consideration, methanol was found to add rapidly and a nearly complete conversion to product *Vd* was obtained. 2-Propanol added more slowly than did ethanol, while the 2-methyl-2-propanol was found to be almost unreactive under a variety of conditions, with the best result being approximately 40% product after 24 h at reflux in the presence of three equivalents of dimethylammonium chloride. Use of Lewis acids like $AlCl_3$ and $TiCl_4$ accelerated the rate of



a, R^1 = Br, R^2 = *t*-Bu, R^3 = H, R^4 = $CHPh_2$

b, R^1 = CH_3O, R^2 = *t*-Bu, R^3 = 1,2,3-triazol-1-yl, R^4 = $CHPh_2$

c, R^1 = CH_3O, R^2 = *t*-Bu, R^3 = 1,2,3-triazol-1-yl, R^4 = $CH_2C_6H_4OCH_3$

d, R^1 = Br, R^2 = CH_3, R^3 = H, R^4 = $CHPh_2$

e, R^1 = Br, R^2 = Et, R^3 = H, R^4 = $CHPh_2$

f, R^1 = Br, R^2 = iPr, R^3 = H, R^4 = $CHPh_2$

g, R^1 = CH_3O, R^2 = CH_3, R^3 = H, R^4 = CH_2CCl_3

SCHEME 1

addition; however, they failed to drive the reaction to completion. Other Lewis acids like $ZnCl_2$ and $SnCl_4$ led to extensive decomposition.

Introduction of the 2α-alkoxymethyl group in the cephem skeleton did not improve the inhibitory activity against human leukocyte elastase. The compound *Vb* had only 39% inhibition at 750 nM while its parent compound *VIb* had an IC_{50} value of 480 nM against HLE.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were recorded with Bruker AC-200E (200 MHz) spectrometer in $CDCl_3$ and are reported relative to TMS as an internal standard.

Benzhydryl 7α-Bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIa*)

To an ice-cooled mixture of 7β-amino-3-methyl-3-cephem-4-carboxylic acid (10.0 g, 0.047 mol), ethanol (270 ml), water (83 ml) and HBr (48%, 56.7 ml) was added $NaNO_2$ (4.67 g, 0.67 mol) in small portions over 25 min and the mixture was stirred at ice-temperature for 2.5 h. Ethanol was removed under reduced pressure and the residual mass was diluted with methylene chloride, washed with water. The aqueous washings were saturated with brine and re-extracted with methylene chloride. The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give 9.8 g (75%) of 7α-bromo-3-methyl-3-cephem-4-carboxylic acid which was directly used for the next step.

To a stirred solution of the crude acid (9.8 g, 0.035 mol) in dry methylene chloride (50 ml) was added dropwise a solution of diphenyldiazomethane (8.21 g, 0.043 mol) dissolved in methylene chloride (50 ml). The mixture was stirred at room temperature for 3 h, washed with 10% $NaHCO_3$ solution, water, brine, and dried (Na_2SO_4). Concentration under reduced pressure gave a brown foam (11.9 g, 76%) which was purified over a silica gel column. Elution of the column with a mixture of hexane–ethyl acetate (85 : 15) gave 8.0 g (51%) of pure benzhydryl 7α-bromo-3-methyl-3-cephem-4-carboxylate. This compound (8.0 g, 0.018 mol) was dissolved in methylene chloride (35 ml), peracetic acid (12.3 g, 0.162 mol) was added slowly and the mixture was stirred at room temperature for 72 h, then washed successively with water, 10% $NaHCO_3$ solution and water. After drying (Na_2SO_4) and concentration, the product was purified over a silica gel column using methylene chloride as eluant. The title compound was obtained as a pale yellow foam (3.35 g, 40%). ^{1}H NMR spectrum: 2.10 s, 3 H (CH_3); 3.80 brs, 2 H (H-2); 4.80 brs, 1 H (H-6); 5.25 brs, 1 H (H-7); 6.95 s, 1 H ($CHPh_2$); 7.2 – 7.6 m, 10 H (arom.)

Benzhydryl 7α-Bromo-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIIIa*)

To a stirred solution of benzhydryl 7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIa*, 2.80 g, 0.0059 mol) in methylene chloride (12 ml) were added dimethylammonium chloride (1.44 g, 0.0176 mol), formaldehyde (37% aqueous solution, 0.61 g, 0.02 mol) and 2-methyl-2-propanol (100 ml), the mixture was heated to reflux for 3 h. Solvent was removed under reduced pressure and the residue was dissolved in methylene chloride, washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified over a silica gel column. Elution of the column with a mixture of hexane–ethyl acetate (75 : 25) gave 2.00 g (69%) of pure product as a white foam. ^{1}H NMR spectrum: 2.10 s, 3 H (CH_3); 4.93 d, 1 H, *J* (6,7) = 1.5 (H-6); 5.33 d, 1 H, *J* (6,7) = 1.5

(H-7); 6.20 d, 1 H, J = 2.0 (=CH_2); 6.70 d, 1 H, J = 2.0 (=CH_2); 6.98 s, 1 H ($CHPh_2$); 7.30 – 7.45 m, 10 H (arom.)

The above reaction conditions always give the *Va* as a minor product. In another experiment, 3.75 g (0.0079 mol) of benzhydryl 7α-bromo-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIa*) was dissolved in dioxane (35 ml); dimethylammonium chloride (1.925 g, 0.024 mol), formaldehyde (37% aqueous solution, 0.830 g, 0.028 mol) and 2-methyl-2-propanol (8.5 ml) were added. The mixture was heated at 70 °C for 2 h. Solvent was removed under reduced pressure. The residue was taken in methylene chloride, washed successively with water, brine, dried (Na_2SO_4) and concentrated to give pure benzhydryl 7α-bromo-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIa*) in 98% yield (3.8 g) as a white solid.

Benzhydryl 7α-Bromo-2α-(1,1-dimethylethoxy)methyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*Va*)

To a solution of benzhydryl 7α-bromo-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIa*, 300 mg, 0.614 mmol) in methylene chloride (1.5 ml) were added dimethylammonium chloride (150 mg, 1.84 mmol) and 2-methyl-2-propanol (10.7 ml). The mixture was heated to reflux for 24 h. Solvent was removed under reduced pressure and the residue was taken in methylene chloride, washed with water, brine and dried (Na_2SO_4). After concentration, the product was purified by preparative TLC. The title compound *Va* was obtained as a pale yellow foam (0.104 g, 30%). For ^{1}H NMR spectrum, see Table I.

Benzhydryl 7α-Bromo-2α-methoxymethyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*Vd*)

To a solution of benzhydryl 7α-bromo-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIa*, 1.0 g, 2.05 mmol) in methylene chloride (24 ml) was added methanol (24 ml) followed by a catalytic amount of $AlCl_3$ (4 mg). The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC. After 6 h of stirring, ^{1}H NMR analysis of the reaction mixture indicates that about 90% of the product has been formed. Extended period of stirring and further addition of $AlCl_3$ did not improve the yield. After usual work up the title compound *Vd* was obtained as an off-white foam (698 mg) which was crystallized twice (benzene–hexane) to give an analytically pure sample (72 mg). For ^{1}H NMR spectrum, see Table I. The compound (*Vd*) could not be purified by silica gel column chromatography; it has a tendency to convert back to 2-*exo*-methylene cephem sulfone (*VIIIa*).

Benzhydryl 7α-Bromo-2α-ethoxymethyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*Ve*)

A solution of benzhydryl 7α-bromo-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIa*, 0.174 g, 0.36 mmol) in a mixture of methylene chloride (5 ml) and anhydrous ethanol (5 ml) was refluxed for 12 h. Solvent was removed under reduced pressure and the residue was taken in methylene chloride, washed successively with water, brine, dried (Na_2SO_4) and concentrated to give a gummy mass (0.161 g, 85%) which was rapidly purified over a silica gel column (elution with hexane–ethyl acetate, 3 : 2). The title compound *Ve* was obtained as a pale yellow foam (100 mg, 53%). On a longer exposure to silica gel column the compound *Ve* converts back to *VIIIa*. For ^{1}H NMR spectrum, see Table I.

Benzhydryl 7α-Bromo-2α-(1-methylethoxy)methyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*Vf*)

To a solution of benzhydryl 7α-bromo-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIa*, 0.5 g, 1.02 mmol) in a mixture of methylene chloride (12 ml) and 2-propanol (12 ml) was

added $AlCl_3$ (14 mg) and the mixture was stirred at room temperature for 6 h. An additional amount of $AlCl_3$ (14 mg) was added and the mixture was heated to reflux for 8 h. After usual work up the product was obtained as a white foam (314 mg) which was purified by column chromatography over a silica gel column. ^{1}H NMR spectrum (see Table I) of this product indicates that it is about 95% pure. The product is contaminated with the starting 2-*exo*-methylene compound *VIIIa*. Attempted purification by crystallization or by preparative TLC was not successful.

Benzhydryl 7α-Methoxy-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIb*)

To 7β-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid (27.2 g, 99.9 mmol) was added water (500 ml) and sodium bicarbonate (9.3 g, 111 mmol); the pH of the mixture was adjusted to 6.5 with 10% NaOH solution, NaN_3 (13.1 g, 201 mmol) and acetone (350 ml) were added. The mixture was heated at 60 °C for 6 h and left stirring overnight at room temperature. Acetone was removed under reduced pressure and the mixture was cooled in an ice-bath, acidified with concentrated HCl to pH 3.5; the precipitated solid was filtered off, dried over P_2O_5 to give 14.3 g (56%) of 7β-amino-3-azidomethyl-3-cephem-4-carboxylic acid which was used for the next step.

To a suspension of this compound (20.7 g, 81 mmol) in a mixture of methylene chloride (250 ml) and dimethyl sulfoxide (250 ml) was added dropwise a solution of diphenyldiazomethane (17.53 g, 90 mmol) in methylene chloride (150 ml). The mixture was stirred at room temperature for 68 h, filtered and the filtrate was concentrated under reduced pressure. The residue was taken into ethyl acetate (250 ml) and washed successively with 10% $NaHCO_3$ solution, water, brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a residue which was purified over a silica gel column (elution with methylene chloride–ethyl acetate, 1 : 1). The product was obtained as a mixture of Δ^2- and Δ^3-isomers (18.4 g, 54%).

To a stirred solution of the isomeric mixture (16 g, 38 mmol) in ethyl acetate (500 ml) at 0 °C was added sodium tungstate dihydrate (1.254 g, 3.8 mmol) and hydrogen peroxide (30% solution, 17.5 ml). After stirring at 0 °C for 15 min, the mixture was stirred at room temperature for 2 h when another portion of hydrogen peroxide (4.4 ml) was added and the resulting mixture was stirred overnight. The mixture was cooled in an ice-bath and sodium bisulfite solution (13 g in 100 ml of water) was added dropwise and the mixture was stirred for 10 min, Na_2CO_3 solution (4 g in 80 ml of water) was added to the above mixture and stirred for 10 min. The organic layer was separated out and the aqueous layer was re-extracted with two portions of ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. To the residue hexane was added and the mixture was stirred with ice-cooling. The precipitated solid was collected by filtration to give 12.2 g (71%) of pure benzhydryl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide. ^{1}H NMR spectrum: 2.35 brs, 2 H (NH_2); 3.70 and 4.01 q, 2 H, J = 18.0 (H-2); 4.25 brs, 2 H (CH_2N_3); 4.80 d, 1 H, J = 5.0 (H-6); 4.95 d, 1 H, J = 5.0 (H-7); 7.05 s, 1 H ($CHPh_2$); 7.40 – 7.65 m, 10 H (arom.).

To an ice-cooled stirred solution of benzhydryl 7β-amino-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide (1.1 g, 2.43 mmol) in methylene chloride (15 ml) was added an ice-cold solution of $NaNO_2$ (184 mg, 2.67 mmol) in water (9 ml); 1.75 M H_2SO_4 (1.1 ml) was added dropwise at such a rate that the temperature was below 0 °C. The mixture was stirred at 0 °C for 1 h; the methylene chloride layer was separated out and the aqueous layer was re-extracted with methylene chloride (2 × 20 ml). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and filtered. To the filtrate, methanol (25 ml) was added and while stirring at room temperature, rhodium acetate dimer (12 mg) was added in one portion. After stirring at room temperature for 1 h, the reaction mixture was filtered through Celite and solvent was removed under reduced pressure. The residue was purified over a silica gel column (elution with hexane–ethyl acetate, 3 : 2) to give pure benz-

hydryl 7α-methoxy-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide (370 mg, 33%). ^{1}H NMR spectrum: 3.56 s, 3 H (OCH_3); 3.71 and 3.99 q, 2 H, *J* = 18.0 (H-2); 4.02 and 4.18 q, 2 H, *J* = 14.0 (CH_2N_3); 4.70 d, 1 H, *J* (6,7) = 1.5 (H-6); 5.19 d, 1 H, *J* (6,7) = 1.5 (H-7); 6.97 s, 1 H ($CHPh_2$); 7.31 – 7.46 m, 10 H (arom.).

A solution of benzhydryl 7α-methoxy-3-azidomethyl-3-cephem-4-carboxylate-1,1-dioxide (3.1 g, 6.62 mmol) in ethylene glycol dimethyl ether (60 ml) was transferred to a steel bomb and cooled to −78 °C; the reaction vessel was flushed with nitrogen for 15 min; 14.0 g of acetylene was taken in the steel bomb and the reaction mixture was heated at 90 °C overnight. The steel bomb was cooled in an ice-bath and the excess acetylene was slowly allowed to evaporate at room temperature. The solvent was removed under reduced pressure. The crude product was purified over a silica gel column (elution with hexane–ethyl acetate, 1 : 1) to give a foam (1.9 g, 58%). Ether was added to the foam and the precipitated solid was collected by filtration. ^{1}H NMR spectrum: 3.55 s, 3 H (OCH_3); 3.65 and 3.97 q, 2 H, *J* = 18.0 (H-2); 4.74 s, 1 H, (H-6); 5.16 s, 3 H (CH_2-triazole + H-7); 7.10 s, 1 H ($CHPh_2$); 7.30 – 7.43 m, 10 H (arom.); 7.51 s, 1 H, and 7.67 s, 1 H (triazole).

Benzhydryl 7α-Methoxy-2-*exo*-methylene-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIIIb*)

To a solution of benzhydryl 7α-methoxy-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide (*VIb*, 1.8 g, 3.85 mmol) in methylene chloride (30 ml) and 2-methyl-2-propanol (70 ml) was added dimethylammonium chloride (940 mg, 11.54 mmol) and formaldehyde solution (37%, 410 mg, 13.5 mmol). The mixture was heated at 80 °C for 1.5 h and the solvent was removed. The residue was taken in methylene chloride, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified over a silica gel column (elution with hexane–ethyl acetate, 1 : 2) to give pure benzhydryl 7α-methoxy-2-*exo*-methylene-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide (*VIIIb*, 910 mg, 49%). ^{1}H NMR spectrum: 3.57 s, 3 H (OCH_3); 4.87 d, 1 H, *J* (6,7) = 2.0 (H-6); 5.01 and 5.47 q, 2 H, *J* = 15.0 (CH_2-triazole); 5.29 d, 1 H, *J* (6,7) = 2.0 (H-7); 6.55 d, 1 H, *J* = 2.6 (=CH_2); 6.64 d, 1 H, *J* = 2.6 (=CH_2); 7.06 s, 1 H ($CHPh_2$); 7.30 – 7.37 m, 10 H (arom.); 7.51 s, 1 H, and 7.58 s, 1 H (triazole). Benzhydryl 7α-methoxy-2α-(1,1-dimethylethoxy)methyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*Vb*) was isolated as a minor component (12%) from this experiment. For ^{1}H NMR spectrum see Table I.

p-Methoxybenzyl 7α-Methoxy-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIc*)

A solution of *p*-methoxybenzyl-7β-amino-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide[7] (800 mg, 1.85 mmol) in dry ethyl acetate was cooled to 10 °C under nitrogen. Isopropyl nitrite (0.247 g, 2.8 mmol) was added to the above solution followed by 3 drops of trifluoroacetic acid. The reaction mixture was further stirred at 10 °C for 1 h and cooled to −5 °C. Rhodium octanoate dimer (18 mg) was dissolved in a mixture of ethyl acetate (10 ml) and anhydrous methanol (2 ml) and the mixture was stirred under nitrogen at 0 °C. After stirring for 30 min, 5 drops of triethylamine was added (the color changes from light green to purple) and the solution was further cooled to −5 °C.

The above two solutions were mixed together at −5 °C and stirred for 2 h. The reaction mixture was diluted with 50 ml of ethyl acetate, made acidic with glacial acetic acid, washed successively with cold water, brine, dried (Na_2SO_4) and concentrated to give a dark brown foam which was purified on a silica gel column (elution with hexane–ethyl acetate, 1 : 1) to give pure *p*-methoxybenzyl-7α-methoxy-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide (*VIc*, 140 mg, 20%). ^{1}H NMR spectrum: 3.54 s, 3 H (OCH_3); 3.65 and 3.93 q, 2 H, *J* = 18.0 (H-2); 3.82 s, 3 H (OCH_3); 4.70 d, 1 H, *J* (6,7) = 1.1 (H-6); 5.08 – 5.40 m, 5 H (CH_2-triazole + CH_2-benzylic + H-7); 6.91 d, 2 H (arom.); 7.37 d, 2 H (arom.); 7.73 s, 2 H (triazole).

TABLE I
Physical and spectral data of 2α-alkoxymethyl cephem sulfones *V*

Compound	Formula (M.w.)	M.p., °C	Calculated/Found			^{1}H NMR spectrum
			% C	% H	% N	
Va	$C_{26}H_{28}BrNO_6S$ (562.5)	foam	55.51 55.44	5.02 5.08	2.49 2.51	1.19 s, 9 H (*tert*-Bu); 1.98 s, 3 H (CH_3); 3.41 brt, 1 H (H-2); 3.68 dd, 1 H, *J* = 2.2 and 10.0 (CH_2O); 4.02 dd, 1 H, *J* = 2.2 and 10.0 (CH_2O); 5.08 d, 1 H, *J*(6,7) = 1.4 (H-6); 5.23 d, 1 H, *J*(6,7) = 1.4 (H-7); 6.96 s, 1 H ($CHPh_2$); 7.18 – 7.46 m, 10 H (arom.)
Vb	$C_{29}H_{32}N_4O_7S$ (580.6)	80 – 82	59.98 59.96	5.56 5.63	9.65 9.56	1.22 s, 9 H (*tert*-Bu); 2.48 brt, 1 H (H-2); 3.54 s, 3 H (OCH_3); 3.83 dd, 1 H, *J* = 2.8 and 10.5 (CH_2O); 4.10 dd, 1 H, *J* = 2.8 and 10.5 (CH_2O); 4.90 and 5.10 q, 2 H, *J* = 15.0 (CH_2-triazole); 4.97 d, 1 H, *J*(6,7) = 1.9 (H-6); 5.20 d, 1 H, *J*(6,7) = 1.9 (H-7); 7.08 s, 1 H($CHPh_2$); 7.30 – 7.37 m, 10 H (arom.); 7.68 s, 1 H (triazole); 7.71 s, 1 H (triazole)
Vc	$C_{24}H_{30}N_4O_8S$ (534.6)	58 – 59	53.92 53.89	5.66 5.64	10.48 10.42	1.21 s, 9 H (*tert*-Bu); 3.28 brt, 1 H (H-2); 3.53 s, 3 H (OCH_3); 3.82 s, 3 H (OCH_3); 3.87 dd, 1 H, *J* = 2.0 and 11.0 (CH_2O); 4.03 dd, 1 H, *J* = 2.0 and 11.0 (CH_2O); 4.91 d, 1 H, *J*(6,7) = 2.0 (H-6); 5.11 d, 1 H, *J*(6,7) = 2.0 (H-7); 4.97 and 5.33 q, 2 H, *J* = 14.9 (CH_2-triazole); 5.28 and 5.59 q, 2 H, *J* = 12.0 (CH_2-benzylic); 6.89 – 7.40 m, 4 H (arom.); 7.72 s, 1 H (triazole); 7.87 s, 1 H (triazole)
Vd	$C_{23}H_{22}BrNO_6S$ (520.4)	85 – 86	53.08 53.14	4.26 4.15	2.69 2.61	2.04 s, 3 H(CH_3); 3.39 brt, 1 H (H-2); 3.40 s, 3 H (OCH_3); 3.75 dd, 1 H, *J* = 2.3 and 10.3 (CH_2O); 3.99 dd, 1 H, *J* = 2.3 and 10.3 (CH_2O); 4.97 d, 1 H, *J*(6,7) = 1.4 (H-6); 5.24 d, 1 H, *J*(6,7) = 1.4 (H-7); 6.92 s, 1 H ($CHPh_2$); 7.28 – 7.49 m, 10 H (arom.)

TABLE I
(*Continued*)

Compound	Formula (M.w.)	M.p., °C	Calculated/Found			^{1}H NMR spectrum
			% C	% H	% N	
Ve	$C_{24}H_{24}BrNO_6S$ (534.4)	foam[a]	–	–	–	1.22 t, 3 H, *J* = 7.0 (OCH_2CH_3); 2.04 s, 3 H (CH_3); 3.42 brt, 1 H (H-2); 3.45 – 3.69 m, 2 H (OCH_2); 3.78 dd, 1 H, *J* = 2.3 and 10.4 (CH_2OEt); 4.04 dd, 1 H, *J* = 2.3 and 10.4 (CH_2OEt); 5.03 d, 1 H, *J*(6,7) = 1.3 (H-6); 5.25 d, 1 H, *J*(6,7) = 1.3 (H-7); 6.94 s, 1 H ($CHPh_2$); 7.26 – 7.50 m, 10 H (arom.)
Vf	$C_{25}H_{26}BrNO_6S$ (548.5)	foam[a]	–	–	–	1.09 d, 3 H, *J* = 6.0 and 1.17 d, 3 H, *J* = 6.0 (iPr); 1.96 s, 3 H, (CH_3); 3.39 brt, 1 H (H-2); 3.50 – 3.65 m, 1 H (iPr); 3.67 dd, 1 H, *J* = 2.2 and 10.6 (CH_2O); 3.99 dd, 1 H, *J* = 2.2 and 10.6 (CH_2O); 5.04 d, 1 H, *J*(6,7) = 1.4 (H-6); 5.21 d, 1 H, *J*(6,7) = 1.4 (H-7); 6.94 s, 1 H ($CHPh_2$); 7.21 – 7.46 m, 10 H (arom.)
Vg	$C_{13}H_{16}Cl_3NO_7S$ (436.7)	foam[a]	–	–	–	2.13 s, 3 H (CH_3); 3.37 brt, 1 H (H-2); 3.43 s, 3 H (OCH_3); 3.56 s, 3 H (OCH_3); 3.77 dd, 1 H, *J* = 1.9 and 10.5 (CH_2O); 4.03 dd, 1 H, *J* = 1.9 and 10.5 (CH_2O); 4.85 and 5.03 q, 2 H, *J* = 12.0 (CH_2CCl_3); 4.90 d, 1 H, *J*(6,7) = 1.6 (H-6); 5.16 d, 1 H, *J*(6,7) = 1.6 (H-7)

[a] Correct elemental analysis could not be obtained. The product is contamined with a trace amount of starting 2-*exo*-methylene compound.

p-Methoxybenzyl 7α-Methoxy-2-*exo*-methylene-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIIIc*)

To a solution of *p*-methoxybenzyl 7α-methoxy-3-[(1,2,3-triazolyl)methyl]-3-cephem-4-carboxylate-1,1-dioxide (*VIc*, 1.27 g, 2.8 mmol) in dry methylene chloride (8 ml) were added dimethylammonium chloride (0.692 g), formaldehyde solution (0.804 ml) and 2-methyl-2-propanol (35 ml). The mixture was heated to reflux for 2 h and solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed successively with water, brine, dried (Na_2SO_4) and evaporated to give a sticky mass which was purified over a silica gel column (elution with hexane–ethyl acetate, 1 : 1). Fast moving component was the minor product, *p*-methoxybenzyl 7α-methoxy-2α-(1,1-dimethylethoxy)methyl-3-methyl-3-cephem-4-carboxylate-1, 1-dioxide (*Vc*, 210 mg, 16%). ^{1}H NMR spectrum see in the Table I. Further elution of the column gave compound *VIIIc*. ^{1}H NMR spectrum: 3.57 s, 3 H (OCH_3); 3.81 s, 3 H (OCH_3); 4.81 d, 1 H, *J* (6,7) = 1.5 (H-6); 5.17 – 5.54 m, 5 H (CH_2-triazole + CH_2-benzylic + H-7); 6.56 d, 1 H, *J* = 2.6 (=CH_2); 6.63 d, 1 H, J = 2.6 (=CH_2); 6.90 d, 2 H (arom.); 7.35 d, 2 H (arom.); 7.66 s, 1 H (triazole); 7.76 s, 1 H (triazole).

2,2,2-Trichloroethyl 7α-Methoxy-3-methyl-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIg*)

2,2,2-Trichloroethyl-7α-methoxy-3-methyl-3-cephem-4-carboxylate[7] (8.7 g, 24.12 mmol) was dissolved in 100 ml of methylene chloride, peracetic acid (51.6 ml) was added dropwise and stirred at room temperature for 18 h. The mixture was washed successively with water, 10% $NaHCO_3$ solution, brine, dried (Na_2SO_4) and concentrated to give a sticky mass. To the sticky mass a mixture of ether–hexane (1 : 1) was added with ice-cooling. The precipitated solid was collected by filtration (9.33 g, 98%). ^{1}H NMR spectrum: 2.17 s, 3 H (CH_3); 3.57 s, 3 H (OCH_3); 4.13 brd, 2 H (H-2); 4.93 s, 1 H and 5.20 s, 1 H (CH_2CCl_3); 5.15 brd, 1 H (H-6); 5.96 brd, 1 H (H-7).

2,2,2-Trichloroethyl 7α-Methoxy-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide[7] (*VIIIg*)

A mixture of 2,2,2-trichloroethyl 7α-methoxy-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIg*, 2.0 g, 5.1 mmol), dimethylammonium chloride (1.24 g, 15.28 mmol), 2-methyl-2-propanol (24 ml), methylene chloride (5 ml) and formaldehyde (1.43 ml, 37% w/v in water) was heated to reflux for 1.5 h. Solvent was removed under reduced pressure and the residue was dissolved in methylene chloride, washed successively with water, brine, dried (Na_2SO_4) and concentrated to give pure 2,2,2-trichloroethyl 7α-methoxy-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIg*, 1.78 g, 86%) as a white solid. ^{1}H NMR spectrum: 2.20 s, 3 H (CH_3); 3.60 s, 3 H (OCH_3); 4.80 d, 1 H, *J* = 14.0 and 5.20 d, 1 H (CH_2CCl_3); 4.90 brs, 1 H (H-6); 5.30 brs, 1 H (H-7); 6.23 brd, 1 H (=CH_2); 6.75 brd, 1 H (=CH_2).

2,2,2-Trichloroethyl 7α-Methoxy-2α-methoxymethyl-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*Vg*)

To a stirred solution of 2,2,2-trichloroethyl 7α-methoxy-2-*exo*-methylene-3-methyl-3-cephem-4-carboxylate-1,1-dioxide (*VIIIg*, 300 mg, 0.74 mmol) in methylene chloride (5 ml) was added methanol (7 ml) and the mixture was refluxed at 50 °C for 5 h. Solvent was removed under reduced pressure and the residue was taken in methylene chloride, washed successively with water, brine, dried (Na_2SO_4) and concentrated to give a white foam (228 mg) which was rapidly purified over a silica gel column. ^{1}H NMR (see Table I) of this product (*Vg*) indicates that it is 95% pure. The product is mixed with the starting 2-*exo*-methylene cephem sulfone (*VIIIg*). Attempted purification by crystallization or by preparative TLC was not successful.

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