Studies related to Cephalosporins. Part 1. Solvolytic Reactions of 3-Bromomethylcephems with Alcohols and Phenols

Fabio Animati, Maurizio Botta, Francesco De Angelis, Andrea Dorigo, Ingeborg Grgurina, and Rosario Nicoletti *

Istituto di Chimica Organica, Università degli Studi di Roma, P. le Aldo Moro 5,00185 Roma, Italy

3-Bromomethyl-3-cephems are solvolyzed by alcohols, similarly to the Δ^2-isomers. The yields are fairly good and this reaction represents a straightforward route to obtain 3-alkoxymethyl-3-cephems.

Both 3-bromomethyl-2-cephems and 3-bromomethyl-3-isomers react with a variety of phenols under solvolytic conditions, giving only *C*-substitution products. This reaction represents the sole example of *C*-alkylation of phenols by an allylic bromide under such mild conditions.

Substitutions at C-3′ of the cephem molecule are of fundamental importance in cephalosporin chemistry, since substituents at this position play a significant role in the biological activity of such antibiotics.[1]

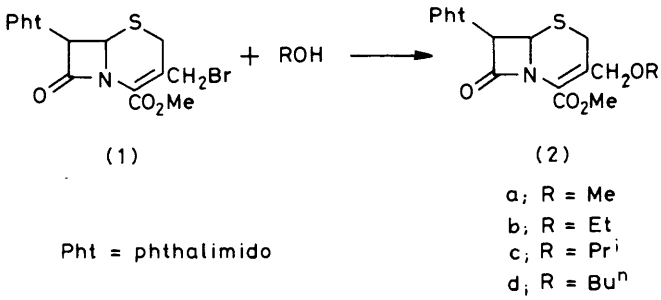
The replacement of the acetoxy group in the 7-ACA† series has given rise to a number of active molecules, and some of them have been successfully marketed.[2] In these displacements the acetoxy group behaves as a good leaving group: to the best of our knowledge there is only one report in which this unusual behaviour is discussed.[3] However, from the very large patent literature it appears that these substitutions are generally possible with highly polarizable (*e.g.* thiolic) nucleophiles, or in the presence of acid catalysts.[4]

Other possible intermediates in the substitution reaction at the 3′-position are the 3-halogenomethyl derivatives such as the 3-bromomethylcephems. In the Δ^2-series these can be obtained through a direct allylic bromination [5] starting from 7-ADCA‡ derivatives, while in the Δ^3-series they can be prepared from 3-*exo*-methylenecephems,[6] the latter being products of the ring enlargement of the penam nucleus according to the Kukolja procedure.[7] Therefore these halogenomethyl derivatives could be intermediates in the route penam ⟶ 7-ACA derivatives. In spite of the above considerations and in contrast with a possible higher reactivity of 3-halogenomethylcephems as compared with that of 3-acetoxymethyl analogues,[8] the former derivatives do not appear to be widely used. Moreover, although they are usually said to be 'important intermediates', only few scattered examples of substitution reactions are reported. The recorded results are sometimes unexpected: poor yields in the displacement of bromine by the acetoxy group [9,10] and poor results with strong nucleophiles like cyanide ions,[11] in the absence of copper(I) ions.

In order to have a better knowledge of the reactivity of 3-halogenomethylcephems, a more thorough investigation of substitution reactions of these compounds is in progress in our laboratories. Here we deal with substitution reactions, not described previously, of 3-bromomethyl-3-cephems with alcohols, as well as the reactions of both Δ^2- and Δ^3-isomers with phenols.

Results and Discussion

3-Bromomethyl-Δ^3-cephalosporins: Reaction with Alcohols.— It has already been shown [5] that bromomethyl-2-cephems react with alcohols giving, in moderate yields, the corresponding alkoxy derivatives under solvolytic conditions. This reaction has been interpreted as the solvolysis of a highly reactive vinylogous α-bromo sulphide.[12] This interpretation does not hold in the case of Δ^3-derivatives. Slow reactions and/or poor yields could be anticipated.



Scheme 1.

Table 1.

Compd.	Reaction time (h)	Yield (%)
(2a)	12	70
(2b)	24	45
(2c)	24	60
(2d)	48	40

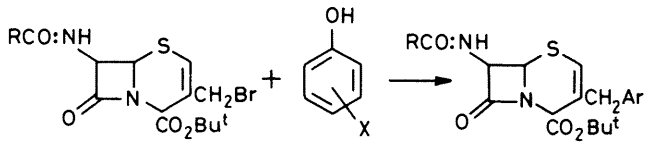
Methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate (1) was prepared in few steps starting from methyl 6-phthalimidopenam-3-carboxylate; Kukolja enlargement of the penam sulphoxide to methyl 3-methylene-7-phthalimidocepham-4-carboxylate *S*-oxide, followed by PBr_3 reduction and bromination with bromine and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) afforded the 3-bromomethyl derivative (1) in overall yield of 59%. These reactions (not previously described in detail) are reported in the Experimental section.

The substrate (1) was submitted to the substitution reaction (Scheme 1) by simply dissolving it in the appropriate anhydrous alcohol. The bromine displacement takes place at room temperature in 24—48 h (see Table 1).

Spectroscopic data of the products (2; a—d) are in full agreement with the assigned structures. No base is required in these reactions: in the case of the substitution with methanol, triethylamine was once included as HBr scavenger, but no improvement in the yields was noted. We also tried the substitution in different acetonitrile (or CH_2Cl_2)/alcohol ratios but the reaction rate dropped with increasing dilution. Higher temperatures also gave lower reaction yields. Finally, we observed no Δ^2-isomers as impurities (easily detectable in the n.m.r. spectra), provided that reactions are carried out under anhydrous conditions.

† 7-ACA = 7-aminocephalosporanic acid

‡ 7-ADCA = 7-aminodesacetoxycephalosporanic acid



(3) R = MeO (4) (5a–d)

a; X = H
b; X = *p*-Me
c; X = *p*-MeO
d; X = *o*-MeO

(6) R = $PhOCH_2$ (4a,d) (7a,d)

Scheme 2.

(8a–c)

The solvolysis of 3-bromomethyl-3-cephems represents a straightforward route to 3-alkoxymethyl-3-cephems; since the reaction of the Δ^2-isomers, which occurs in lower yields,[5] requires the subsequent isomerization of the double bond, its overall yield is very poor, as compared with that of the route here described.

3-Bromomethyl-2- and -3-cephems: Reactions with Phenols.— Substrate (1), previously described, was used in these experiments, while two different Δ^2-bromomethyl derivatives (6) (t-butyl 3-bromomethyl-7-phenoxyacetamido-2-cephem-4-carboxylate) [13] and (3) (t-butyl 3-bromomethyl-7-methoxycarbonylamino-2-cephem-4-carboxylate) were prepared. Compound (3) was prepared starting from 7-ADCA, which was acylated following the procedure already described for 7-ACA, to afford 3-methyl-7-methoxycarbonylamino-3-cephem-4-carboxylic acid. Esterification–isomerization of the latter was performed following a modification of the method described.[13] Bromination of the ester [13] afforded (3). The choice of the methoxycarbonyl protecting group was suggested by the absence of signals in the aromatic proton region in the ^1H n.m.r. spectrum of (3).

Substrate (3) was allowed to react with an excess (molar ratio 1 : 4) of phenols (4a—d) in acetonitrile at room temperature, over a 4 h period (see Scheme 2). Each reaction gave a main product (5a—d) always with a common by-product separated by chromatography as a more polar compound.

The latter was identified as t-butyl 3-hydroxymethyl-7-methoxycarbonylamino-2-cephem-4-carboxylate (the corresponding hydroxymethyl cephem) through its spectroscopic properties (n.m.r., i.r.) and those of the corresponding 3-acetoxymethyl-2-cephem, obtained by acetylation. Since the hydroxymethyl derivative was present also in reactions with carefully dried samples of phenol, it probably arises from hydrolysis of the starting material during work-up.

The mass spectra of the products (5a—d) showed molecular peaks corresponding to coupling products between substrate (3) and phenols (4) minus HBr. N.m.r. spectra showed broad singlets at δ 3.38 which could be assigned to allyl-benzyl protons as reported in the literature.[4] In the i.r. spectra a band corresponding to the hydroxy group was present; this band disappeared in the spectra of all compounds after acetylation. Moreover compound (5a) showed a well-defined AB type pattern in the aromatic region of the ^1H n.m.r. spectrum, so indicating a *para* C-substitution.

Table 2.

Compd.	Ar	Reaction time (h)	Yield (%)	3′-H [δ($CDCl_3$) − δ(C_5D_5N)]
(5a)	*p*-HOC_6H_4	5	45	+0.06
(5b)	2-HO-5-MeC_6H_4	5	48	−0.36
(5c)	2-HO-5-$MeOC_6H_3$	5	39	−0.35
(5d)	2-HO-3-$MeOC_6H_3$	5	28	0.00
(7a)	*p*-HOC_6H_4	5	35	
(7d)	2-HO-3-$MeOC_6H_3$	5	30	
(8a)	*p*-HOC_6H_4	24	60	−0.10 0.00
(8b)	2-HO-5-MeC_6H_3	48	55	−0.45 −0.35
(8c)	2-HO-5-$MeOC_6H_3$	48	48	−0.42 −0.37

Similar results were obtained starting from substrate (6). Here too, some of the hydrolysis product, t-butyl 3-hydroxymethyl-7-phenoxyacetamido-2-cephem-4-carboxylate, was obtained along with the 3-benzyl derivatives, (7a—d).

No isomerization of the double bond was observed in all cases considered. The yields of the products obtained are shown in Table 2.

The reactivity of the 3-bromomethyl derivative (1) was found to be slightly different. Very slow reactions were observed when compound (1) was allowed to react with phenols in acetonitrile solutions (Scheme 2). Only by using a large excess of phenols (*ca.* 1 : 20 molar ratio) in the presence of a small amount of solvent (acetonitrile) in order to have a clear solution, the bromine-free cephem derivatives arising from a substitution reaction (8a—c) could be isolated in reasonably good yield (see Table 2).

In the n.m.r. spectrum of (8a) an AB system centred at δ 3.97 could correspond to an allylic phenoxy substituted methylene or to an allylic phenyl substituted methylene. However, in the aromatic proton region an AB type pattern suggested the presence of a *para*-substituted phenol. The differences in the pattern of signals due to the benzyl methylene between Δ^2- and Δ^3-isomers have already been observed.[4] In the case of Δ^2-compounds a broad singlet appears, whilst an AB is relative to the methylene of Δ^3-isomers.

The i.r. spectrum of (8a) showed the hydroxy absorption band which was no longer present in the spectrum of the acetyl derivative, obtained by treatment with Ac_2O–pyridine. Similar properties were shown by the products (8b,c), each of which had the expected ^1H n.m.r. and mass spectral characteristics.

Therefore, the bromomethyl derivatives (Δ^2 and Δ^3) react with phenols, giving products of *C*-alkylation (no *O*-alkylation products were detected: see the Experimental section) without any added catalyst. Generally, allylic bromides react with phenols in the absence of external catalysts only at high temperature and then give mixtures of *ortho* and *para* substituted products together with some *O*-alkylation product.[14]

There are other examples of aromatic substitutions at the C-3′ atom where similar products were obtained, but the displaced group was acetoxy,[4] trifluoroacetoxy,[4] or carbamoyloxy [15] in Δ^2-derivatives, or acetoxy in a Δ^3-derivative.[3]

Further spectroscopic evidence in order to demonstrate the substitution pattern of the aromatic moiety was found. The [$^2H_5$]pyridine induced shift of proton resonances [δ($CDCl_3$) − δ(C_5D_5N)] for simple phenols was first pioneered by Demarco

et al.[16] This technique was subsequently applied by G. Delle Monache and co-workers [17] on more complex molecules to establish the location of the substituents in the proximity of the phenolic hydroxy group.

The [$^2H_5$]pyridine induced shift of the 3'-methylene indicates whether the group is *ortho* with respect to the phenolic hydroxy group ($\Delta\delta$ = 0.3—0.4) or *para* (no appreciable shift). Relevant results are reported in Table 2.

Other n.m.r. data support the identified structures. The substitution product (5d) of guaiacol after acetylation, shows in its ^1H n.m.r. spectrum an aromatic pattern identical with that exhibited by eugenol acetate, prepared for comparison purposes. The ^{13}C n.m.r. spectrum of the acetate of (5d) as compared to that of a similar cephalosporin, described by Peter *et al.*,[4] shows identical shifts, relative to the carbon atoms of the aromatic moiety.

The ^1H n.m.r. spectra of products (8b) and (8c) were compared with those of appropriate models available in the literature * in order to assign chemical shifts to the aromatic protons (see Experimental section). In both cases only one aromatic proton is dramatically shifted in [$^2H_5$]pyridine ($\Delta\delta$ 0.50 p.p.m.) whilst two protons show a less intense shift difference (*ca.* 0.20 p.p.m.), so indicating one proton *ortho* to the hydroxy and two protons in the *meta* position.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 257 instrument and n.m.r. spectra at 90 MHz on a Perkin-Elmer R32 instrument. Low- and high-resolution mass spectra were recorded on an AEI MS 12 spectrometer and a 7070F VG spectrometer respectively. Preparative and analytical t.l.c. were performed on pre-coated Merck-Kieselgel 60 F254 plates. Visualisation was performed with u.v. light and H_2SO_4 and heat.

Column chromatography was performed using Merck Kieselgel 60 (70—230 mesh ASTM). All anhydrous solvents were distilled from phosphorus pentoxide, except *N,N*-dimethylformamide which was dried over calcium hydride and distilled immediately before use.

Solvolysis products, prepared on a small scale, were identified through their spectroscopic properties, and the exact mass measurement of the molecular peak, when appropriate.

Purity was checked by t.l.c. and confirmed by n.m.r. spectroscopy. The procedures for the isolation of the products have not been optimized.

Methyl 6-Phthalimidopenam-3α-carboxylate 1-Oxide.—Methyl 6-phthalimidopenam-3α-carboxylate (6 g, 16.6 mmol) was dissolved in dry chloroform (270 ml). The solution was cooled in an ice-bath, and a solution of *m*-chloroperbenzoic acid (90%; 3.5 g, 18 mmol) in dry chloroform (200 ml) was added dropwise with constant stirring during 1 h. The reaction mixture was stirred for a further hour, and was then worked up by treatment with 5% sodium metabisulphite, saturated aqueous sodium hydrogencarbonate, and finally saturated sodium chloride. The solution was dried (Na_2SO_4) and evaporated to dryness to afford methyl-6-phthalimidopenam-3α-carboxylate 1-oxide (5.5 g, 90%) as a white foam; $\nu_{max.}$ ($CHCl_3$) 1 820 (lactam C=O), 1 760 (ester C=O), and 1 745 cm^{-1} (imide C=O); δ_H(90 MHz; $CDCl_3$) 1.3 and 1.7 (each 3 H, s, CMe_2), 3.81 (3 H, s, CO_2Me), 4.57br (1 H, s, 4-H), 4.8 (1 H, d, *J* 4.5 Hz, 6-H), 5.88 (1 H, d, *J* 4.5 Hz, 7-H), and 7.7—8.0 (4 H, m, aromatic); *m/z* 376 (M^+).

(R)- *and* (S)-*Methyl 3-Methylene-7-phthalimidocepham-4-carboxylate 1-Oxide.*—Methyl 6-phthalimidopenam-3α-carboxylate 1-oxide (2 g, 54 mmol) was suspended in dry carbon tetrachloride (110 ml) and *N*-chlorosuccinimide (730 mg, 56 mmol) was added. The solution was refluxed for *ca.* 70 min and then cooled to 25 °C. A solution of tin tetrachloride (1.2 ml, 60 mmol) in dry carbon tetrachloride (10 ml) was added dropwise during 2 min. After 0.5 h the reaction mixture was cooled to 0 °C, diluted with chloroform and neutralized with saturated sodium hydrogencarbonate. The aqueous phase was repeatedly extracted with chloroform and the combined organic layers were washed with water, treated with saturated aqueous sodium chloride, and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography ($CHCl_3$–$MeCO_2Et$, 8 : 2) yielded methyl 3-methylene-7-phthalimidocepham-4-carboxylate 1-oxide (1.5 g, 75%) as a mixture of *R* and *S* sulphoxides, in the ratio of *ca.* 2 : 1. An analytical sample (200 mg) of the mixture was chromatographed on silica gel ($CHCl_3$–$MeCO_2Et$, 8 : 2) and pure samples of the two sulphoxides were thus obtained: *R* sulphoxide, $\nu_{max.}$ ($CHCl_3$) 1 810 (lactam C=O), 1 750 (ester C=O), and 1 745 cm^{-1} (imide C=O); δ_H(90 MHz; $CDCl_3$) 3.62 and 4.12 (2 H, q, *J* 12 Hz, 2-H), 3.85 (3 H, s, CO_2Me), 4.88 (1 H, d, *J* 4.5 Hz, 6-H), 5.25br (1 H, s, 4-H), 5.58 (2 H, d, *J* 5.5 Hz, C=CH_2), 5.97 (1 H, d, *J* 4.5 Hz, 7-H), and 7.7—8.0 (4 H, m, aromatic); *m/z* 374 (M^+); *S* sulphoxide, $\nu_{max.}$ ($CHCl_3$) 1 810 (lactam C=O), 1 750 (ester C=O), and 1 745 cm^{-1} (imide C=O); δ_H(90 MHz; $CDCl_3$) 3.63br (2 H, s, 2-H), 3.82 (3 H, s, CO_2Me), 4.9 (1 H, d, *J* 4.5 Hz, 6-H), 5.32 (1 H, s, C=CH), 5.46br (1 H, br s, 4-H), 5.64 (1 H, d, *J* 4.5 Hz, 7-H), 5.77 (1 H, s, C=CH), and 7.7—8.0 (4 H, m, aromatic); *m/z* 374 (M^+).

Methyl 3-Bromomethyl-7-phthalimido-3-cephem-4-carboxylate (1).—(*R*)- and (*S*)-Methyl-3-methylene-7-phthalimidocepham-4-carboxylate 1-oxide (1 g, 2.7 mmol) was dissolved in dry *N,N*-dimethylformamide (DMF) (6 ml) under a nitrogen atmosphere in a two-necked flask fitted with a dropping funnel. The solution was cooled in an ice-bath and the dropping funnel was filled with dry DMF (6 ml). Phosphorus tribromide (0.4 ml., 3.3 mmol) was added and the solution was rapidly added to the solution in the flask with constant stirring. An orange-yellow precipitate formed within 2 min. After *ca.* 0.5 h the reaction mixture was poured into an Erlenmeyer flask containing 5% sodium hydrogencarbonate (40 ml) kept in an ice-bath. Methyl 3-methylene-7-phthalimidocepham-4-carboxylate was precipitated and collected as pale yellow crystals (650 mg) by filtration. The mother liquors were extracted with ethyl acetate, and the extract washed repeatedly with water and treated with saturated aqueous sodium chloride. The solution was dried (Na_2SO_4) and evaporated to dryness to afford more of the same compound (90 mg) as a colourless foam; total yield 740 mg (75%). The m.p. of the crude product was 182—185 °C, $\nu_{max.}$($CHCl_3$) 1 800 (lactam C=O) and 1 740 cm^{-1} (ester and imide C=O); δ_H(90 MHz; $CDCl_3$) 3.38 and 3.63 (2 H, q, *J* 15 Hz, 2-H), 3.80 (3 H, s, CO_2Me), 5.32br (3 H, s, C=CH_2 and 4-H), 5.46 (1 H, d, *J* 4.5 Hz, 6-H), 5.67 (1 H, d, *J* 4.5 Hz, 7-H), and

* In choosing the models, we considered the 3-methylene-3-cephem group equivalent to a methyl group, the hydroxy in $CDCl_3$ equivalent to a methoxy group, and the hydroxy in C_5D_5N similar to a nitro group, as far as ^1H n.m.r. shifts of the aromatic protons are concerned.

Thus the spectrum of (8b) in $CDCl_3$ was compared with that of 2,4-dimethylanisole, while that of (8b) in C_5D_5N was compared with the spectrum of 3-methyl-4-nitroanisole. The spectrum of (8c) in $CDCl_3$ was compared with that of 2,5-dimethoxytoluene, whilst the spectrum of (8c) in C_5D_5N was compared with that of 4-nitroanisole. All spectra of the model compounds were found in 'The Sadtler Handbook of Proton NMR Spectra,' Sadtler-Heyden, 1978.

7.6—7.95 (4 H, m, aromatic); *m/z* 358 (M^+). Recrystallization with methanol resulted in isomerization of the product to methyl 3-methyl-7-phthalimido-3-cephem-4-carboxylate, m.p. 178—179 °C (from $CHCl_3$–n-hexane, 1 : 1) (Found: C, 56.65; H, 3.85; N, 7.6. Calc. for $C_{17}H_{14}N_2O_5S$: C, 57.00; H, 3.94; N, 7.80).

Methyl 3-methylene-7-phthalimidocepham-4-carboxylate (500 mg, 1.4 mmol) obtained from the reaction described previously, was dissolved in anhydrous methylene chloride (8 ml), and the solution cooled in a bath of dry ice and acetone. At the same time a solution of DBU (0.3 ml, 2 mmol) in dry CH_2Cl_2 (9.7 ml) was prepared. A solution of bromine (0.1 ml, 2 mmol) in dry CH_2Cl_2 (1 ml) was added to the one containing DBU. The yellow solution formed was added dropwise to the solution of the cepham during 5—10 min with constant stirring. The temperature was allowed to rise to −10 °C to −5 °C over 3 h. The reaction mixture was then diluted with chloroform and treated with 1M HCl (5 ml). The mixture was allowed to reach room temperature and the organic layer was separated from the aqueous phase which was then extracted with chloroform. The combined organic layers were treated with 5% sodium bisulphite, saturated sodium hydrogencarbonate, then water and finally a saturated solution of sodium chloride. The solution was dried (Na_2SO_4) and evaporated to dryness to afford chromatographically pure methyl 3-bromomethyl-7-phthalimido-3-cephem-4-carboxylate (500 mg, 85%), $\nu_{max.}$($CHCl_3$) 1 810 (lactam C=O) and 1 745 cm^{-1} (ester and imide C=O); δ_H(90 MHz; $CDCl_3$) 3.44 and 3.73 (2 H, q, *J* 15 Hz, 2-H), 3.86 (3 H, s, CO_2Me), 4.48 and 4.80 (2 H, q, *J* 10 Hz, 3′-H), 5.18 (1 H, d, *J* 4.5 Hz, 6-H), 5.82 (1 H, d, *J* 4.5 Hz, 7-H), and 7.7—8.00 (4 H, m, aromatic); *m/z* 436 (M^+).

General Procedure for the Substitution Reaction of (1) *with Alcohols.*—In a typical experiment, the cephem (1) (220 mg, 0.5 mmol) was dissolved in the appropriate anhydrous (ex. sodium metal) alcohol (20 ml) at room temperature. After the reaction was completed (t.l.c. n-hexane–ethyl acetate, 1 : 1), the solution was evaporated to dryness, to yield the corresponding 3-alkoxymethyl derivative (2). The solid product was purified by p.l.c. (n-hexane–ethyl acetate, 1 : 1) and recovered from silica by elution with ethyl acetate. The products were identified on the basis of their spectroscopic properties. They all exhibited very similar i.r. spectral characteristics, *viz.* $\nu_{max.}$($CHCl_3$) 1 805 (lactam C=O) and 1 745 cm^{-1} (ester and imide C=O).

Methyl 3-methoxymethyl-7-phthalimido-3-cephem-4-carboxylate (2a). This compound has the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 3.35 (3 H, s, OMe), 3.55 (2 H, d, *J* 4.5 Hz, 2-H), 3.86 (3 H, s, CO_2Me), 4.53 (2 H, d, *J* 5.5 Hz, 3′-H), 5.14 (1 H, d, *J* 4.5 Hz, 6-H), 5.77 (1 H, d, *J* 4,5 Hz, 7-H), and 7.7—8.0 (4 H, m, aromatic); *m/z* 388 (M^+).

Methyl 3-ethoxymethyl-7-phthalimido-3-cephem-4-carboxylate (2b). This compound has the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.18 (3 H, t, *J* 6 Hz, CH_2CH_3), 3.48 (2 H, q, *J* 6 Hz, CH_2CH_3), 3.51 (2 H, d, *J* 4 Hz, 2-H), 3.85 (3 H, s, CO_2Me), 4.55 (2 H, d, *J* 2 Hz, 3′-H), 5.05 (1 H, d, *J* 4.5 Hz, 6-H), 5.70 (1 H, d, *J* 4.5 Hz, 7-H), and 7.7—7.95 (4 H, m, aromatic); *m/z* 402 (M^+).

Methyl 3-isopropoxymethyl-7-phthalimido-3-cephem-4-carboxylate (2c). This compound shows the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.13 [6 H, d, *J* 5 Hz, $CH(CH_3)_2$], 3.68 [1 H, m, $OCH(CH_3)_2$], 3.50 (2 H, d, *J* 4 Hz, 2-H), 3.84 (3 H, s, CO_2Me), 4.53 (2 H, d, *J* 2 Hz, 3′-H), 5.06 (1 H, d, *J* 4.5 Hz, 6-H), 5.70 (1 H, d, *J* 4.5 Hz, 7-H), and 7.7—8.0 (4 H, m, aromatic); *m/z* 416 (M^+).

Methyl 3-n-butoxymethyl-7-phthalimido-3-cephem-4-carboxylate (2d). This compound shows the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 3 Hz, CH_2CH_3), 1.30—1.70 (4 H, m, $CH_2CH_2CH_3$), 3.51 (2 H, t, *J* 6 Hz, OCH_2), 3.57 (2 H, d, *J* 3 Hz, 2-H), 3.83 (3 H, s, CO_2Me), 4.53 (2 H, d, *J* 2 Hz, 3′-H), 5.13 (1 H, d, *J* 4.5 Hz, 6-H), 5.77 (1 H, d, *J* 4.5 Hz, 7-H), and 7.7—8.0 (4 H, m, aromatic); *m/z* 430 (M^+).

General Procedure for the Substitution Reactions of (1) *with Phenols* (4*a*—*c*).—In a typical experiment, the cephem (1) (440 mg, 1 mmol) was dispersed in the appropriate freshly distilled phenol (2 g, *ca.* 20 mmol) and then anhydrous acetonitrile (1.5 ml) was added. The mixture was warmed gently to fusion and left under nitrogen for 24—48 h at room temperature. After the reaction was completed (t.l.c.: n-hexane–ethyl acetate, 1 : 1), the crude mixture was purified by column chromatography, by first eluting unchanged phenol and MeCN with n-hexane–ethyl acetate (9 : 1) and then the cephem derivative (8a—c) with n-hexane–ethyl acetate (1 : 1). The product was further purified by p.l.c. and the compounds recovered from silica by eluting with ethyl acetate to give white amorphous solids.

No other products were detected by t.l.c. under different conditions: in the case of the reaction of the cephem (1) with phenol to afford (8a), the absence of the *O*-alkylation product (having a higher R_F value) was checked by comparison of the reaction mixture with an authentic sample of the latter, available in our laboratory.*

Identification of the products was based on their spectroscopic properties. They all showed very similar i.r. spectral characteristics: *viz.* $\nu_{max.}$($CHCl_3$) 3 500—3 200 (OH), 1 805 (lactam C=O), and 1 745 cm^{-1} (ester and imide C=O).

Methyl 3-(4-hydroxybenzyl)-7-phthalimido-3-cephem-4-carboxylate (8a). This compound has the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 2.93 and 3.53 (2 H, q, *J* 15 Hz, 2-H), 3.77 and 4.2 (2 H, q, *J* 14 Hz, 3′-H), 3.87 (3 H, s, CO_2Me), 5.12 (1 H, d, *J* 4.5 Hz, 6-H), 5.68 (1 H, d, *J* 4.5 Hz, 7-H), 6.72 [2 H, d, *J* 9 Hz, *o*-H(OH)], 7.08 [2 H, d, *J* 9 Hz, *m*-H(OH)], and 7.7—7.85 (4 H, m, aromatic) (Found: M^+, 450.0887. $C_{23}H_{18}N_2O_6S$ requires M^+, 450.0886).

Methyl 3-(2-hydroxy-5-methylbenzyl)-7-phthalimido-3-cephem-4-carboxylate (8b). This compound has the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 2.22 (3 H, s, Me-Ar), 3.10 and 3.67 (2 H, q, *J* 16 Hz, 2-H), 3.71 and 4.20 (2 H, q, *J* 14 Hz, 3′-H), 3.93 (3 H, s, CO_2Me), 5.10 (1 H, d, *J* 4.5 Hz, 6-H), 5.71 (1 H, d, *J* 4.5 Hz, 7-H), 6.77 [1 H, s, *o*-H(OH)], 6.87 [2 H, m, m-H(OH)], and 7.7—8.0 (4 H, m, aromatic) (Found: M^+ 464.1046. $C_{24}H_{20}N_2O_6S$ requires M^+, 464.1042).

Methyl 3-(2-hydroxy-5-methoxybenzyl)-7-phthalimido-3-cephem-4-carboxylate (8c). This compound shows the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 3.10 and 3.65 (2 H, q, *J* 15 Hz, 2-H), 3.75 and 4.20 (2 H, q, *J* 16 Hz, 3-H), 3.75 (3 H, s, MeO-Ar), 3.95 (3 H, s, CO_2Me), 5.11 (1 H, d, *J* 4.5 Hz, 6-H), 5.75 (1 H, d, *J* 4.5 Hz, 7-H), 6.73 [3 H, br s, *o*-H(OH) and *m*-H(OH)], and 7.7—7.95 (4 H, m, aromatic) (Found: M^+ 480.0993. $C_{24}H_{20}N_2O_7S$ requires M^+ 480.0991).

3-Methyl-7-methoxycarbonylamino-3-cephem-4-carboxylic Acid.—To a solution of 7-ADCA (6.63 g, 30 mmol) in acetone (140 ml), water (140 ml) and triethylamine (4.6 ml, 32 mmol), cooled to −10 °C, methyl chloroformate (2.3 ml, 30 mmol) was added dropwise. The mixture was stirred for 2 h at room temperature, a few drops of triethylamine being added during this period in order to maintain a clear solution. The acetone was removed under reduced pressure and the mixture,

* Work in progress.

layered with ethyl acetate and cooled, was acidified with 2M-HCl. The organic layer was separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with water and dried (Na_2SO_4). The solution was evaporated to dryness to afford 3-*methyl*-7-*methoxycarbonylamino*-3-*cephem*-4-*carboxylic acid* (7 g, 85%), δ_H[90 MHz; $(CD_3)_2SO$] 2.00 (3 H, s, 3-H), 3.43 (2 H, d, *J* 6 Hz, 2-H), 3.6 (3 H, s, MeO-CO), 5.2 (1 H, d, *J* 4.0 Hz, 6-H), 5.4 (1 H, q, *J* 4 Hz, 7-H), and 8.2 (1 H, d, *J* 8 Hz, NH).

t-Butyl 3-*Methyl*-7-*carbomethoxyamino*-2-*cephem*-4-*carboxylate*.—To a suspension of 3-methyl-7-methoxycarbonylamino-3-cephem-4-carboxylic acid (5.38 g, 0.02 mol) in anhydrous benzene (800 ml) and (DMF, 2 drops) cooled to 0 °C, oxalyl chloride (3.4 ml, 0.04 mol) was added dropwise. After the mixture had been stirred for 1 h at 60 °C, *ca.* two-thirds of the solvent were evaporated. The acid chloride thus obtained was added dropwise during 3 h to a cooled mixture of t-butyl alcohol (15 g, 0.24 mol), triethylamine (4.5 ml, 0.035 mol), and benzene (130 ml). The benzene solution was then washed with water, 3% HCl, water again, and finally dried (Na_2SO_4). The solution was evaporated to dryness and the crude product was purified by column chromatography [light petroleum (b.p. 60—80 °C.ethyl acetate, 6 : 4]. Chromatographically pure t-butyl 3-methyl-7-methoxycarbonylamino-2-cephem-4-carboxylate (4.8 g, 66%) was obtained, m.p. (uncorrected) 98—100 °C (needles, ethyl acetate–n-hexane) (Found: C, 50.95; H, 6.10; N, 8.35. $C_{14}H_{20}N_2O_5S$ requires C, 51.20; H, 6.15; N, 8.15) δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 1.9 (3 H, s, 3′-H), 3.6 (3 H, s, MeO-CO), 4.65 (1 H, s, 4-H), 5.25 (1 H, d, *J* 4 Hz, 6-H), 5.6 (1 H, d, *J* 4 Hz, 7-H), and 5.82 (1 H, br, s, 2-H).

3-*Methyl*-7-*phenoxyacetamido*-3-*cephem*-4-*carboxylic Acid and t-Butyl* 3-*Methyl*-7-*phenoxyacetamido*-2-*cephem*-4-*carboxylate*. These were prepared according to the procedures described in the literature.[18,13] The allylic bromides (6) and (3) were obtained as unstable oils by bromination of the corresponding esters as described in the literature [5] for (6) which, however, had not been isolated; (6) and (3) were identified on the basis of their n.m.r. spectral characteristics: t-butyl 3-bromomethyl-7-phenoxyacetamido-2-cephem-4-carboxylate (6), δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 4.0—4.4 (2 H, q, *J* 10 Hz, 3′-H), 4.55 (2 H, s, OCH_2CO), 5.2 (1 H, br s, 4-H), 5.35 (1 H, d, *J* 4 Hz, 6-H), 5.7 (1 H, q, *J* 4 Hz, 7-H), 6.5 (1 H, br s, 2-H), and 6.9—7.4 (5 H, m, aromatic); t-butyl 3-bromomethyl-7-methoxycarbonylamino-2-cephem-4-carboxylate (3), δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 3.7 (3 H, s, MeO-CO), 4.0—4.4 (2 H, q, *J* 10 Hz, 3′-H), 5.18 (1 H, br, s, 4-H), 5.3 (1 H, d, *J* 4 Hz, 6-H), 5.55 (1 H, q, *J* 4 Hz, 7-H), and 6.5 (1 H, br s, 2-H).

General Procedure for the Reaction of Allylic Bromides (6) *and* (3) *with Phenols* (*Table* 2).—The bromide (6) or (3) was dissolved in acetonitrile and the phenol was added (molar ratio 1 : 4). After 4 h at room temperature, water was added to the mixture and the whole extracted with ethyl acetate (×3). The combined organic extracts were washed with water, 5% sodium hydrogen carbonate, water again, and then finally dried (Na_2SO_4). After solvent evaporation, the product was separated by column chromatography (n-hexane–ethyl acetate, 6 : 4). T.l.c. analyses showed that the only by-product was the 3-hydroxymethyl-2-cephem. The products were identified on the basis of their spectroscopic properties. They all presented very similar i.r. spectra: the characteristic absorption bands were as follows: $\nu_{max.}$($CHCl_3$) 3 570 (OH), 3 400 (NH), 2 900—3 000 (CH), 1 780 (lactam C=O), 1 740 (ester C=O), 1 690 (amide C=O), and 1 620 cm^{-1} (C=C).

t-Butyl 3-(4-*hydroxybenzyl*)-7-*methoxycarbonylamino*-2-*cephem*-4-*carboxylate* (5a). This compound shows the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 3.4 (2 H, br s, 3′-H), 3.7 (3 H, s, MeO-CO), 4.7 (1 H, br s, 4-H), 5.3 (1 H, d, *J* 4 Hz, 6-H), 5.45 (1 H, q, *J* 4 Hz, 7-H), 5.85 (1 H, br s, 2-H), and 6.7—7.0 (4 H, m, aromatic) (Found: M^+, 420.1353. $C_{20}H_{24}N_2O_6S$ requires M^+, 420.1355).

t-Butyl 3-(2-*hydroxy*-5-*methylbenzyl*)-7-*methoxycarbonylamino*-2-*cephem*-4-*carboxylate* (5b). This compound shows the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 2.25 (3 H, s, Me-Ar), 3.45 (2 H, br s, 3′-H), 3.7 (3 H, s, MeO-CO), 4.8 (1 H, s, 4-H), 5.2 (1 H, d, *J* 4 Hz, 6-H), 5.5 (1 H, q, *J* 4 Hz, 7-H), 5.85 (1 H, br s, 2-H), and 6.7—7.0 (3 H, m, aromatic) (Found: M^+, 434.1508. $C_{21}H_{26}N_2O_6S$ requires M^+, 434.1511).

t-Butyl 3-(2-*hydroxy*-5-*methoxybenzyl*)-7-*methoxycarbonylamino*-2-*cephem*-4-*carboxylate* (5c). This compound has the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me_3)C$], 3.45 (2 H, br s, 3′-H), 3.67 (3 H, s, Me-OAr), 3.7 (3 H, s, MeO-CO), 4.78 (1 H, s, 4-H), 5.25 (1 H, d, *J* 4 Hz, 6-H), 5.5 (1 H, q, *J* 4 Hz, 7-H), 5.85 (1 H, br, s 3-H), and 6.6—6.8 (3 H, m, aromatic) (Found: M^+, 450.1459. $C_{21}H_{26}N_2O_7S$ requires M^+, 450.1460).

t-Butyl 3-(4-*hydroxy*-3-*methoxybenzyl*)-7-*methoxycarbonylamino*-2-*cephem*-4-*carboxylate* (5d). This compound has the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 3.3 (2 H, br s, 3′-H), 3.7 (3 H, s, MeO-CO), 3.85 (3 H, s, MeO-Ar), 4.7 (1 H, br s, 4-H), 5.3 (1 H, d, *J* 4 Hz, 6-H), 5.45 (1 H, d, *J* 4 Hz, 7-H), 5.90 (1 H, br s, 2-H), and 6.55—6.9 (3 H, m, aromatic) (Found: M^+, 450.1459. $C_{21}H_{26}N_2O_7S$ requires M^+, 450.1460).

t-Butyl 3-(4-*hydroxybenzyl*)-7-*phenoxyacetamido*-2-*cephem*-4-*carboxylate* (7a). This compound shows the following spectroscopic properties: δ($_H$90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 3.45 (2 H, br s, 3′-H), 4.55 (2 H, s, OCH_2CO), 4.65 (1 H, br s, 4-H), 5.3 (1 H, d, *J* 4 Hz, 6-H), 5.7 (1 H, q, *J* 4 Hz, 7-H), 5.9 (1 H, br s, 2-H), and 6.8—7.8 (9 H, m, aromatic).

t-Butyl 3-(4-*hydroxy*-3-*methoxybenzyl*)-7-*phenoxyacetamido*-2-*cephem*-4-*carboxylate* (7d). This compound shows the following spectroscopic properties: δ_H(90 MHz; $CDCl_3$) 1.5 [9 H, s, $(Me)_3C$], 3.5 (2 H, br s, 3′-H), 3.85 (3 H, s, MeO-Ar), 4.55 (2 H, br s, OCH_2CO), 4.65 (1 H, br s, 4-H), 5.3 (1 H, d, *J* 4 Hz, 6-H), 5.7 (1 H, d, *J* 4 Hz, 7-H), 5.9 (1 H, br s, 2-H), and 6.6—7.4 (8 H, m, aromatic).

Acknowledgements

We are grateful to the Consiglio Nazionale delle Ricerche (C.N.R.) for funds provided, and to the C.N.R.-Area della Ricerca di Roma-Servizio Spettrometria di Massa and to Mr. Enzo Brancaleoni for the high-resolution mass spectra.

References

1 M. Gorman and C. W. Ryan in 'Cephalosporins and Penicillins,' H. Flynn ed., Academic Press, N.Y., 1972, pp. 554 ff.
2 R. Bucourt in 'Recent Advances in the Chemistry of β-Lactam Antibiotics.' Proceedings of the Second International Symposium, 1980, G. I. Gregory (ed.), pp. 4—5.
3 J. D. Cocker, D. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly, and G. A. Somerfield, *J. Chem. Soc.*, 1965, 5015.
4 H. Peter, H. Rodriguez, B. Muller, W. Sibral, and H. Bickel, *Helv. Chim. Acta*, 1974, **57**, 2024.
5 J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen, and R. T. Vasileff, *J. Med. Chem.*, 1971, **14**, 113.
6 G. A. Koppel, M. D. Kinnick, and L. J. Nummy, *J. Am. Chem. Soc.*, 1977, **99**, 2822.
7 S. Kukolja, S. R. Lammert, M. R. B. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, 1976, **98**, 5040.

8 C. F. Murphy and J. A. Webber, ref. 1, p. 155.
9 G. A. Koppel, M. D. Kinnick, and L. J. Nummy in ' Recent Advances in the Chemistry of β-Lactam Antibiotics,' J. Elks (ed.), Cambridge University Press, Cambridge, 1976, p. 107.
10 J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Am. Chem. Soc.*, 1969, **91**, 5674.
11 J. A. Webber and R. T. Vasileff, *J. Med. Chem.*, 1971, **14**, 1136.
12 C. F. Murphy and J. A. Webber, ref. 1, p. 170.
13 C. F. Murphy and R. E. Koehler, *J. Org. Chem.*, 1970, **35**, 2429.
14 D. G. Kundiger and H. Pledger, Jr., *J. Am. Chem. Soc.*, 1956, **78**, 6101.
15 S. Karady, T. Y. Cheng, S. H. Pines, and H. Sletzinger, *Tetrahedron Lett.*, 1974, 2629.
16 P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, 1968, **90**, 5480.
17 R. A. De Lima and G. Delle Monache, *Rend. Accad. Naz. 40* [*Quaranta*], Ser. V, 1977—78, **3**, 181.
18 R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. José, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, 1971, **36**, 1259.

Received 6th December 1982; *Paper* 2/2028