Uncommon Formation of Spiro Orthoesters in the Bromomethoxylation Reaction of a 4-[(Aroyloxy)methyl]-3-cephem Derivative

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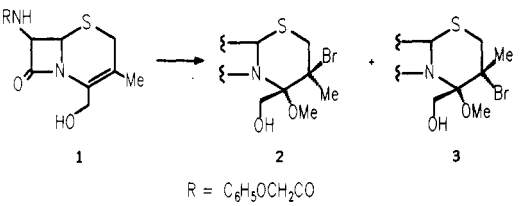
The reaction of 4-[((*p*-nitrobenzoyl)oxy)methyl]-3-cephem derivative **4** with bromine in methanol afforded a mixture of the 3-bromo-4-methoxy adducts **5** and **6** and of the unexpected 4-spiro orthoesters **7** and **8**. The structure and configuration of **7** and **8** were demonstrated through the determination of the solid-state structure of **7** and by ^1H and ^{13}C NMR studies and chemical transformations. The mechanism and the stereochemical outcome of the reaction are discussed.

The study of the reactivity of the functionalities present in the bicyclic nucleus of cephalosporins has been considered for some time as a valid way to arrive at new β-lactam compounds more complex than those of natural origin. In the course of a study carried out on this subject, the double bond of the 4-(hydroxymethyl)-3-cephem derivative **1** was found to react easily with bromine in methanol, affording exclusively the *trans*-3β-bromo-4α-methoxy (**2**) and the *cis*-3α-bromo-4α-methoxy adduct (**3**) (Scheme I).[1,2] These two compounds (**2** and **3**) present the same regiochemistry on C(3) and C(4) and the same stereochemistry on the methoxy-bearing carbon (C(4)): they differ only in their configuration on the carbon atom (C(3)) to which the bromine is linked. The complete regiospecificity of the reaction and the formation of the syn adduct (**3**) were explained by assuming that the attack of the electrophilic bromine from both sides of the molecule of the 3-cephem derivative (**1**) leads to intermediates with a high degree of carbocationic character on the carbon (C(4)), which undergoes the subsequent attack of the nucleophilic methanol.[2] As regards the different stereochemical behavior of the reaction that leads to the anti (**2**) or syn adduct (**3**), depending on whether the bromine attack comes from the β or α side of the molecule, respectively, it was not possible to offer any rationalization.[2]

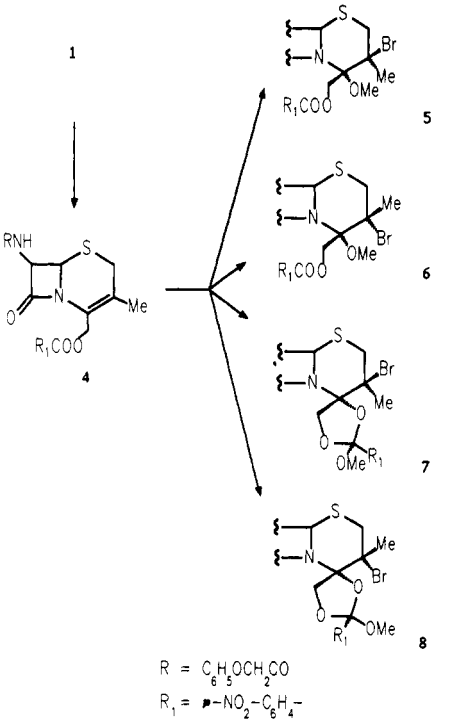
The peculiar behavior of the bromomethoxylation reaction of compound **1** might have been due either to some of the various functionalities adjacent to the unsaturated system, which constitutes the center of the reaction, or to the considerable steric hindrances present in the molecule.

In order to evaluate the influence of the alcoholic hydroxyl on the carbon adjacent to the olefinic double bond of **1** on the behavior of the nucleophilic step of the reaction, we decided to subject a cephem derivative, structurally similar to **1**, but without the free hydroxyl, to the same reaction carried out on **1**.

Scheme I



Scheme II



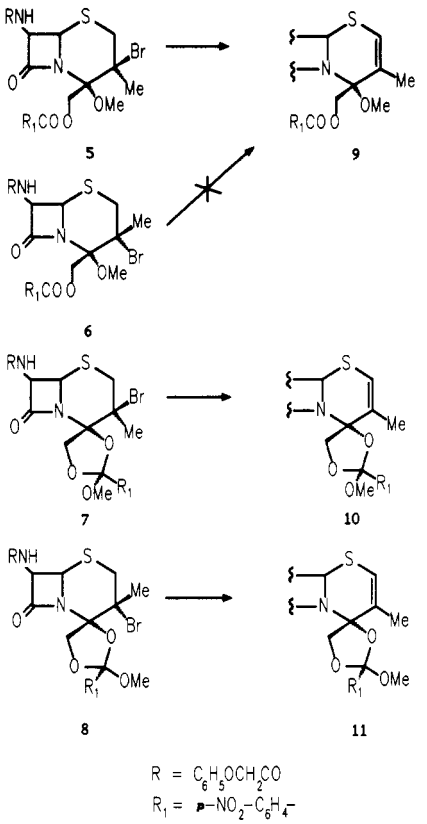
The present paper describes the synthesis and the reaction with bromine in methanol of the *p*-nitrobenzoyl ester of **1** (**4**), together with the study and the structural characterization of the reaction products obtained (**5–8**).

(1) Balsamo, A.; Domiano, P.; Macchia, B.; Macchia, F.; Orlandini, E.; Rossello, A. *J. Chem. Res., Synop.* **1984**, 226; *J. Chem. Res., Miniprint* **1984**, 2155.

(2) Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Scatena, P.; Domiano, P. *J. Org. Chem.* **1986**, *51*, 540.

0022-3263/91/1956-2148$02.50/0

Scheme III



Chemistry

The *p*-nitrobenzoyl ester **4** was obtained by treating the alcohol **1** with *p*-nitrobenzoyl chloride in pyridine (see Scheme II). The reaction of **4** with Br_2 in methanol was carried out under the same conditions in which the alcohol **1** had afforded the bromomethoxy adducts **2** and **3**.[1,2] This reaction gave a mixture composed of the cepham derivatives **5** and **6** and the spirodioxolane derivatives **7** and **8** in a ratio of about 2.6:1.2:4.7:1.5. These compounds were isolated chromatographically.

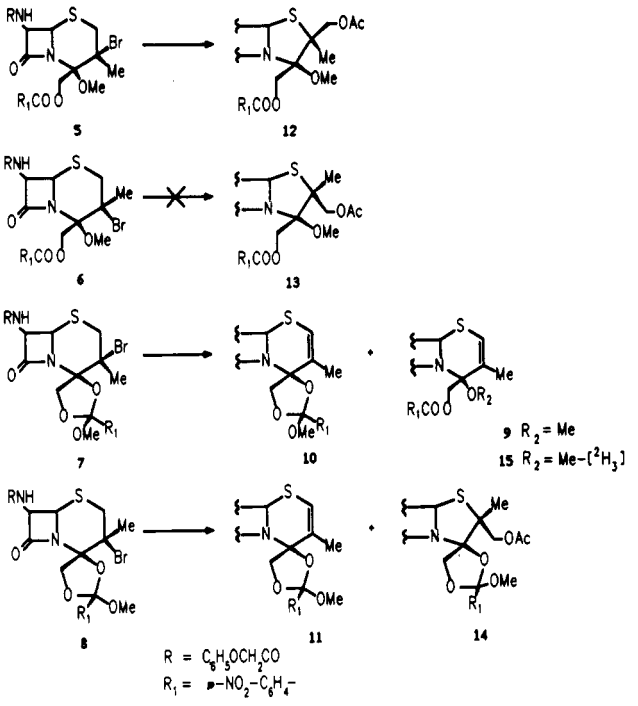
The structures of **5** and **6** were determined by means of a comparison with authentic samples[2] obtained by *p*-nitrobenzoylation of the corresponding alcohols **2** and **3**.

As regards the new cepham derivatives **7** and **8**, the IR and ^1H NMR spectroscopic data indicated only their bromomethoxycepham nature and the existence of a structural analogy between them, but they did not permit a complete definition of their structure. Compound **7** proved to be solid and capable of affording crystals suitable for crystallographic analysis. However, in spite of various attempts, we were initially unable to resolve its structure completely. In an attempt to obtain further information about the structures of compounds **7** and **8**, some reactions were carried out on all the products obtained. Some of these reactions had been useful for structural demonstrations of other β-lactam compounds.[2,3]

The bromocephams **5–8** were treated with a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature (Scheme III). Under these conditions, while the bromomethoxy adduct **5** and the spirodioxolanes **7** and **8** gave the corresponding 2-cephem derivatives **9–11**, respectively, compound **6** was recovered unchanged.

When the compounds **7** and **8** were treated with silver acetate in glacial acetic acid at 100 °C, under the same conditions that had led[2] from the cepham derivatives **5** and **6** to the penicillin derivatives **12** and **13**, respectively, only complex mixtures of non-β-lactam products were obtained. When the reaction with silver acetate was performed in MeOH at 60 °C (Scheme IV), instead of in AcOH at 100 °C, compound **7** gave a mixture of the 2-cephem derivatives **10** and **9**, in a ratio of about 2:1, while the spiro derivative **8** afforded a mixture of the Δ^2-cephalosporin (**11**) and penicillin (**14**), in a proportion of approximately 3:1. Under the same reaction conditions, the anti adduct (**5**) afforded the already known penam derivative **13**,[2] also obtained in the reaction in AcOH,[2] while the syn isomer (**6**), instead of giving the expected penicillin **13**, proved to be completely nonreactive.

Scheme IV



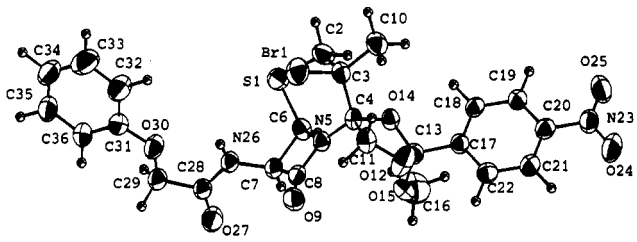


Figure 1. ORTEP II plot (50% probability level for thermal ellipsoids) of the X-ray structure of **7** showing the crystallographic atom-numbering scheme.

In order to test their stability, compounds **7–11** and **14** were heated in MeOH at 60 °C. Under these conditions, while **10** was quantitatively converted to the ester **9**, the other compounds (**7**, **8**, **11**, and **14**) proved to be completely stable. When **10** was heated in MeOH-d_4, the MeO-d_3 analogue of **9** (**15**) was obtained.

Recently, a new attempt to resolve the crystal structure of **7**, using a new collection of experimental data obtained with a well-developed crystal of a new preparation, has been successful. An ORTEP plot of the X-ray structure of **7**, showing the crystallographic numbering scheme, is given in Figure 1.

As can be seen from Figure 1, compound **7** presents, in its molecular structure, a cepham nucleus substituted on

(3) Balsamo, A.; Crotti, P.; Macchia, B.; Macchia, F.; Nannini, G.; Dradi, E.; Forgione, A. *J. Org. Chem.* **1976**, *41*, 2150.

Table I. ^{1}H NMR Data of Cepham Derivatives 5–8

compd	3-Me	H-2β	H-2α	OMe	5′-H_A	5′-H_B	CH_2OCO	H-6	H-7	p-$NO_2C_6H_4$
5[2]	2.00 s	2.63 d 10[a]	3.71 d 17[a]	3.42 s			5.21, 5.30 2 d	5.03 d	5.68 dd	8.15, 8.30 AA′BB′
6[2]	2.07 s	2.81 d 15[a]	4.12 d	3.50 s			5.03, 5.06 2 d	5.06 d	5.61 dd	8.17, 8.30 AA′BB′
7	1.45 s	2.65 d 5[a]	3.33 d 20[a]	3.14 s	4.37 d 20[a]	5.33 d –5[a]		5.18 d	5.65 dd	7.70, 8.25 AA′BB′
8	2.00 s	2.81 d 19[a]	3.47 d	3.29 s	4.40 d 20[a]	5.45 d –4[a]		4.60 d	5.10 dd	7.70, 8.23 AA′BB′

[a] NOE values (%) obtained by irradiation of the 3-methyl singlet.

the C(3) by an atom of bromine and linked, via the C(4), to a spirodioxolane ring;[4] the C(13) of the latter is in turn substituted by a *p*-nitrophenyl moiety and a methoxyl, which thus give rise to an uncommon cyclic orthoester function. The tetrahydrothiazine portion of the molecule exists in a half-chair conformation; the β-lactam ring is practically planar, while the dioxolane ring adopts an envelope form in which the O(14) atom is displaced by 0.386 Å from the plane through the other four atoms. The bromine atom has the same β orientation as the phenoxyacetamido side chain, while the *p*-nitrophenyl group and the methoxyl are situated, respectively, on the opposite side and on the same side as the β-lactam nucleus.

As far as distances and angles are concerned, the values for **7** do not differ substantially from those obtained for the corresponding molecular portion of the bromomethoxycepham derivative **2**.[1] The most significant differences concern the C(3)–C(4) and the C(3)–C(10) bond distances (1.551 and 1.563 Å, respectively, vs 1.577 and 1.518 Å for **2**) and the distance between N(5) and the plane of its three bonded carbon atoms C(4), C(6), and C(8) (0.047 vs 0.115 Å for **2**).

Once the structure and the configuration of the orthoester **7** had been demonstrated by means of crystallographic analysis, it was possible to assign the structure and configuration to **8**, too, on the basis of a comparison between its spectral characteristics and those of **7** and the already known **5** and **6**.[2]

The presence in **8** of a cyclic orthoester system linked to the C(4), analogous to the one revealed by **7**, was deduced on the basis of the finding that the absorption band attributable to the stretching of an ester carbonyl is absent in the IR spectrum of **8**, as it is in that of **7**. Furthermore, the structural analogy of the molecular portion linked to the C(4) of **7** and **8** can also be seen from a comparison of the chemical shifts of the ^{1}H NMR signals of the protons of their *p*-nitrophenyl moiety with those of the signals of the corresponding protons of **5** and **6** (see Table I). In **7** and **8**, as a result of the different effect of their orthoester moiety with respect to that of the ester function of **5** and **6**, the two protons of the *p*-nitrophenyl system situated adjacent to the orthoester nucleus resonate at higher fields (7.70 ppm) than the corresponding protons of **5** and **6** near to the ester carbonyl (8.15 and 8.17 ppm, respectively).

Independent support for the structure assigned to the portion linked to C(4) of **8** comes from the comparison of the ^{13}C NMR data of **5**,[2] **6**,[2] and **7** and **8** (see the Experimental Section). The chemical shifts for OMe, C(4), and C(5′) (C(11) in the ORTEP plot of Figure 1) signals are very different between the couples **5**, **6** and **7**, **8**. Probably as a result of the shielding effect of the adjacent aromatic ring, the OMe signal of **7**, **8** reveals a position at higher fields than in the couple **5**, **6**; on the contrary, the quaternary C(4) and the C(5′) carbons of the spiro derivatives **7** and **8** exhibit a very dramatic downfield shift in comparison with the corresponding carbons of the nonspirocyclized compounds **5** and **6**.[7]

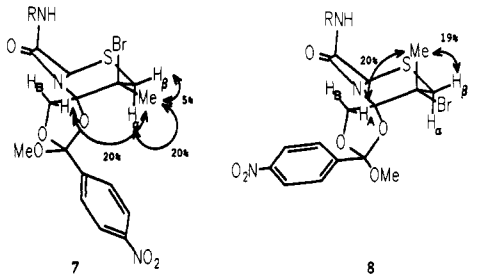


Figure 2.

The study of the internal nuclear Overhauser effects (NOE)[8] between the 3-Me and the H-2 and H-5′ in **7** and **8** made it possible to assign both the configurations on C(3) and C(4) of **8** and the configuration in solution of its tetrahydrothiazine system. Only a 3β-Me isomer presenting the *S* configuration on C(4), like the one shown by **8**, in its half-chair conformation (see Figure 2), is in agreement with the presence of two relatively strong NOE between the 3β-Me and the H-2β (19%) and between the same methyl and one of the two H-5′ (H_A) of the spirodioxolanic CH_2 (20%) and with the absence of a NOE between the same 3β-Me and the H-2α. Compound **7**, which with respect to **8** possesses the opposite configuration on C(3) and the same configuration on C(4), presents NOE between the 3α-Me and both the hydrogens H-2α and H-2β (20% and 5%, respectively) and between the same 3α-Me and one of the two H-5′ (H_A), which were to be expected on the basis of the knowledge of its structure, configuration, and conformation in the solid state. Both for **7** and for **8**, the negative NOE found between the 3-Me and the other H-5′ atom (H_B) may be justified by the existence of a system Me··H_A··H_B,[9] in which the negative effect of saturation would be transmitted to H_B via the H_A proton spatially fixed in the spirodioxolanic cyclic system.[10]

(4) Search on the Cambridge Crystallographic Structural Database,[5] accessed through the Servizio Italiano Diffusione Dati Cristallografici (CNR-Parma), revealed that the only spiro compound with a bicyclic β-lactam structure found was a spirooxirane derivative.[6]

(5) Allen, F. H.; Bellard, S.; Brice, M. D.; Cartwright, B. A.; Doubleday, A.; Higgs, H.; Hummelink, T.; Hummelink-Peters B. G.; Kennard, O.; Motherwell W. D. S.; Rodgers, J. R.; Watson, D. G. *Acta Crystallogr., Sect. B* **1979**, *B35*, 2331.

(6) Siriwardane, U.; Chu, S. S. C. *Acta Crystallogr., Sect. C* **1989**, *C45*, 531.

(7) In the couple **5**, **6**, the 3α-Me carbon atom of **5** resonates at lower field than the 3β-Me carbon of **6**, whereas in the couple **7**, **8** both 3α- and 3β-methyl carbons resonate at very similar chemical shifts. This may be due to the presence in **7** and **8** of a spirodioxolanic structure allowing the *p*-nitrophenyl group to exert a different shielding effect on their 3-methyl carbon (see Figure 2).

(8) See, for example: Demarco, P. V.; Nagarajan, R. *Cephalosporins and Penicillins: Chemistry and Biology*; Flynn, E. H., Ed.; Academic Press: New York, 1972; Chapter 8.

(9) (a) Balaram, P.; Bothner-By, A. A.; Dadok, J. *J. Am. Chem. Soc.* **1972**, *94*, 4015. (b) Kalman, J. R.; Williams, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 897.

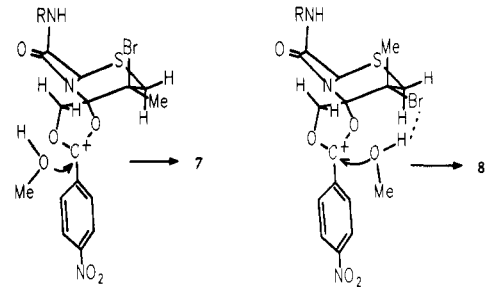
The two orthoesters 7 and 8, which present a different configuration on C(3) and the same configuration on C(4), might or might not have differed also in the stereochemistry of the orthoester carbon C(2′). If, however, 7 and 8 had presented the same configuration on C(2′), their dehydrobromination should have led to a single Δ^2-cephem derivative, i.e., 10. On the contrary, the two orthoesters 7 and 8, treated with DBU, afforded different dehydrohalogenation products (10 and 11, respectively). As the crystallographic study of 7 had demonstrated unequivocally the *S* configuration of its C(2′), it was thus possible to assign the *R* configuration to the same carbon of 8.

Some of the most evident differences in the chemical shift values of the signals of some protons of 7 and 8 can be explained by bearing in mind their stereostructures indicated in Figure 2. The relatively high-field absorption for 3-Me in 7 (see Table I) is in agreement with the great proximity of the anisotropic aromatic cone of the *p*-nitrophenyl group, as clearly shown also in the solid state. For compound 8, instead, in which an inverted situation is present on C(2′), the aromatic ring, situated completely on the opposite side, has no effect on the 3-Me group, now influencing the H-6 and H-7 hydrogens that both undergo the shielding ring current effect (see Table I).

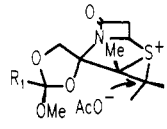
The Δ^2-cephem nature of 9–11 is clear for the presence in their ^{1}H NMR spectra of a signal that can be attributed to the olefinic proton linked to C(2), which exhibits an allylic coupling with the methyl group linked to C(3). The configuration on C(4) of compound 9 may be assumed to correspond to that of 5, bearing in mind that, in the dehydrohalogenation reaction of 5 that leads to 9, the C(4) chiral center is not involved. The structure of the molecular portion linked to the C(4) of 10 and 11 might or might not have differed from that of 7 and 8, respectively, as a result of a possible dioxolane ring opening of the orthoester function. However, comparison of the spectral characteristics of 10 and 11 with those of the corresponding starting compounds 7 and 8 made it possible to assign also to 10 and 11 a spirodioxolanic structure like that of 7 and 8. In particular, similar to observations for 7 and 8, the IR spectra of 10 and 11 present the only stretching bands of the β-lactam and amide functions in the 6-μm region. Furthermore, in the ^{1}H NMR spectra of 10 and 11, the signals of the protons of the *p*-nitrophenyl system exhibit a pattern that is practically the same as that of the same protons in the spiro derivatives 7 and 8. The fact, then, that in the dehydrohalogenation reaction of 7 and 8 to 10 and 11 the spirodioxolanic portion maintains its integrity made it possible to assign also to its two chiral centers (C(4) and C(2′)) of 10 and 11 the same stereochemistry as the corresponding starting compounds 7 and 8.

The penicillin nature of 14 was established on the basis of the not very high value (12.2 Hz) of the geminal coupling constant of the methylene protons of the CH_2OAc group and of the high value (1789 cm^{-1}) of the stretching frequency of the β-lactam C=O.[2,11,12] The presence in 14 of the dioxolanic structure was deduced from the pattern of the ^{1}H NMR signals of the protons of the *p*-nitrophenyl moiety linked to the orthoester carbon (see above), which is practically identical with that of the orthoesters 10 and 11. The configurations on the two chiral carbons of the spirodioxolanic nucleus of 14 were assumed to correspond to those of the bromocepham derivative 8, bearing in mind that in the ring contraction reaction leading from 8 to 14 these two chiral centers are not involved. As regards the configuration on the C(2) of 14, this was assumed on the basis of the hypothesis that, similar to what has previously been admitted for the transformations 5 → 12 and 6 → 13 in the silver acetate/acetic acid reaction,[2] the ring contraction of 8 proceeds via the stereoselective formation of the intermediate episulfonium ion 16,[2] which undergoes the regiospecific attack of the nucleophilic acetate on the methylenic thiiranium carbon.

Scheme V



17 18



16

R = $C_6H_5OCH_2CO$
R_1 = p-NO_2-C_6H_4-

In the case of the bromomethoxylation reaction of 1 (see the introduction and Scheme I), the nucleophilic step of the reaction, initiated by the positive bromine, consisted of the stereoselective attack of the methanol on the C(4) of the intermediate bromonium or bromocarbenium ion that is formed by the attack of the bromine from the β or the α side of the molecule, with the formation of the bromomethoxy adducts syn (2) and anti (3), respectively.[1,2] In the bromination reaction in methanol of 4, instead (see Scheme II), besides the normal addition products 5 and 6, structurally corresponding to 2 and 3, more complex products are formed, such as the orthoesters 7 and 8. The latter two compounds may be imagined to derive from the intramolecular attack on C(4) of the carbonyl oxygen of the *p*-nitrobenzoic group, with the formation of intermediate dioxolenium ions[13] 17 and 18 (see Scheme V), which may subsequently be attacked by the methanol on the positively charged carbon.

The bromination reaction in methanol of 4 presents, as far as the two reaction centers C(3) and C(4) are concerned, regio and stereochemical behavior analogous to that of the same reaction of alcohol 1.[1,2] During the nucleophilic step of the reaction, the attack of the nucleophilic agent (methanol or carbonyl oxygen of the ester group) takes place exclusively on C(4) and proves to be completely anti or syn stereoselective, depending on whether the attack of the bromine comes from the β or the α side of the molecule, respectively. Furthermore, it should be pointed out that the attack of the methanol on the intermediate

(10) NOE experiments carried out on 5 and 6 showed the presence of the expected NOEs: Appreciable NOEs were found for 5 between 3-Me and both H-2β and H-2α (10% and 17%, respectively) and for 6 between 3-Me and H-2α (17%) (see Table I).

(11) Barton, D. H. R.; Comer, F.; Greig, D. G. T.; Sammes, P. G.; Cooper, C. M.; Hewitt, G.; Underwood, W. G. E. *J. Chem. Soc. C* **1971**, 3540.

(12) Tsushima, T.; Tanida, H. *J. Org. Chem.* **1980**, *45*, 3205.

(13) (a) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A*; Plenum Press: New York, 1984; Chapter 5, p 289. (b) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1943**, *65*, 613.

dioxolenium ions 17 and 18 proves to be completely stereoselective, with the formation of 7 from 17 and 8 from 18. In the case of the formation of 7, the stereoselectivity of the attack might be attributed to the unfavorable steric effects of the α-oriented methyl group linked to C(3) with respect to an attack of methanol from the opposite direction to the one indicated in 17. In the formation of 8, on the other hand, the stereoselective attack of methanol might be due to possible interactions of the bromine on C(3) with molecules of methanol, as indicated in 18, which would entropically favor the attack on the C(2′) of one of these molecules rather than that of others that are not coordinated, thus leading to the formation of 8.

In conclusion, the results of this study would appear to indicate that the presence or absence of a free hydroxyl group in compounds of type 1 is not decisive in determining the regio- and stereochemical pattern of the bromination reaction in methanol of these compounds.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra for comparison of compounds were taken of paraffin oil mulls on a Perkin-Elmer Model 1310 instrument and those for the determination of C=O stretching bands with a Perkin-Elmer Model 257 double-beam grating spectrophotometer using a NaCl cell of 1-mm optical length in dried $CHBr_3$. ^1H NMR spectra of all coupounds were routinely detected with a Varian CFT-20 instrument operating at 80 MHz in a ca. 2% solution of $CDCl_3$, against Me_4Si as the internal standard. The relative percentages of compounds 5–11 and 14 were calculated on the basis of the integrals of the 3-Me singlets (for 5–8), 3-Me doublets (for 9–11), and 2β-Me singlet (for 14) in the ^1H NMR spectra of the crude reaction mixtures. The ^1H NMR spectral study of 7 and 8 and the determination of the spectral parameters of 5 and 6 at high fields (see Table I) were performed with a Bruker CXP-200 FT instrument. NOE experiments were performed in carefully degassed $CDCl_3$ solutions. ^{13}C NMR spectra were taken in $CDCl_3$ solutions with a Varian CFT-20 or with a Bruker CXP-200 instrument operating at 20 or 50 MHz, respectively. Preparative TLCs were performed on 0.5- or 2.0-mm silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under UV light (254 nm). Preparative MPLC was carried out with 230–400-mesh silica gel. Evaporations were made in vacuo (rotating evaporator). $MgSO_4$ was always used as a drying agent.

3-Methyl-4-[((*p*-nitrobenzoyl)oxy)methyl]-7β-(phenoxyacetamido)-3-cephem (4). A stirred solution of 1[1] (3.27 g, 9.8 mmol) in dry CH_2Cl_2 (82 mL) and anhydrous pyridine (3.0 mL) was treated dropwise at 0 °C with a solution of *p*-nitrobenzoyl chloride (2.32 g, 12.5 mmol) in anhydrous CH_2Cl_2 (33 mL). The solution was stirred for 30 min at the same temperature and for 18 h at room temperature and then diluted with CH_2Cl_2. The resulting solution was washed (5% aqueous HCl, 10% aqueous $NaHCO_3$, H_2O), filtered, and evaporated to give an oily residue that was submitted to flash chromatography using a 60:40 AcOEt–hexane mixture as the eluent to yield 4 as a semisolid product (4.0 g), which by crystallization from $CHCl_3$–hexane gave pure 4 (3.5 g, 74%): mp 162–164 °C; IR (Nujol) ν 1764 cm^{-1} (β-lactam C=O); ^1H NMR ($CDCl_3$) δ 1.95 (s, 3, Me), 3.02 and 3.53 (2 d, 2, J = 17.0 Hz, SCH_2), 4.55 (s, 2, CH_2CO), 5.00 (d, 1, J = 5.0 Hz, CHS), 5.32 (s, 2, CH_2OCO), 5.82 (dd, 1, J = 5.0 and 9.0 Hz, NHC*H*), 8.23 (br s, 4, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{23}H_{21}N_3O_7S$: C, 57.13; H, 4.38; N, 8.69. Found: C, 57.20; H, 4.40; N, 8.43.

Reaction of 4 with Bromine in Methanol. A solution of bromine (1.57 g, 9.82 mmol) in anhydrous MeOH (48 mL) was added dropwise to a cooled (0 °C) and stirred suspension of 4 (2.40 g, 4.97 mmol) and $CaCO_3$ (2.40 g, 24 mmol) in anhydrous MeOH (240 mL). When the addition was complete, the reaction mixture was left for 30 min at the same temperature, treated with solid $Na_2S_2O_3$ until the disappearance of the bromine color, and then evaporated. The residue was triturated with $CHCl_3$, and then the resulting suspension was washed three times with brine, filtered, and evaporated to yield an oily residue (2.20 g) consisting of the bromomethoxy adducts 5 and 6 and of the orthoesters 7 and 8 in a ratio of about 2.6:1.2:4.7:1.5 (^1H NMR). The crude oil was subjected to preparative MPLC on silica gel, eluting with a 5:4:1 hexane–AcOEt–CH_2Cl_2 mixture. The first fractions obtained gave pure **(4*S*,2′*S*)-3α-bromo-3-methyl-7β-(phenoxyacetamido)-4-spiro-4′-[2′-methoxy-2′-(*p*-nitrophenyl)-1′,3′-dioxolane]cepham (8)** (0.16 g, 5.4%), as an oil: IR ($CHBr_3$) ν 1777 (β-lactam C=O), 1690 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 2.81 and 3.47 (2 d, 2, J = 15.4 Hz, SCH_2), 4.40 and 5.45 (2 d, 2, J = 10.0 Hz, $CH_2OC(O)_2C$), 4.60 (d, 1, J = 4.8 Hz, CHS), 5.10 (dd, 1, J = 4.8 and 9.8 Hz, NHC*H*), 7.70 and 8.23 (AA′BB′ system, 4, J = 9.0 Hz, *p*-$NO_2C_6H_4$); ^{13}C NMR δ 27.7 (3-Me), 38.3 (C(2)), 50.9 (OMe), 59.9 (C(3)), 69.3 (C(5′)), 91.4 (C(4)). For other spectral data see Table I. Anal. Calcd for $C_{24}H_{24}BrN_3O_8S$: C, 48.49; H, 4.07; Br, 13.44; N, 7.07. Found: C, 48.69; H, 4.18; Br 13.28; N, 6.90.

The middle fractions yielded a solid residue (0.35 g) that by crystallization from acetone–hexane afforded pure **(4*S*,2′*R*)-3β-bromo-3-methyl-7β-(phenoxyacetamido)-4-spiro-4′-[2′-methoxy-2′-(*p*-nitrophenyl)-1′,3′-dioxolane]cepham (7)** (0.24 g, 8.1%): mp 131–132 °C; IR ($CHBr_3$) ν 1775 (β-lactam C=O), 1688 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 2.65 and 3.33 (2 d, 2, J = 15.4 Hz, SCH_2), 4.37 and 5.33 (2 d, 2, J = 10.4 Hz, $CH_2OC(O)_2C$), 5.18 (d, 1, J = 4.8 Hz, CHS), 5.65 (dd, 1, J = 4.8 and 9.8 Hz, NHC*H*), 7.70 and 8.25 (AA′BB′ system, 4, J = 9.0 Hz, *p*-$NO_2C_6H_4$); ^{13}C NMR δ 27.2 (3-Me), 37.9 (C(2)), 50.9 (OMe), 62.2 (C(3)), 69.7 (C(5′)), 91.4 (C(4)). For other spectral data see Table I. Anal. Calcd for $C_{24}H_{24}BrN_3O_8S$: C, 48.49; H, 4.07; Br, 13.44; N, 7.07. Found: C, 48.62; H, 4.20; Br, 13.18; N, 6.79.

From the final fractions, a mixture was obtained of the bromomethoxy adducts 5 and 6 (0.26 g), which were separated by preparative TLC, eluting with 1:1.5 ethyl acetate–hexane. Extraction with $CHCl_3$ of the two bands observed yielded pure 6[2] (0.058 g, 2.0%) and 5[2] (0.097 g, 3.3%) from the upper and the lower bands, respectively. 5: ^{13}C NMR δ 28.8 (3-Me), 38.2 (C(2)), 52.0 (OMe), 63.8 (*C*H_2OCO), 65.0 (C(3)), 87.8 (C(4)). 6: ^{13}C NMR δ 26.8 (3-Me), 37.8 (C(2)), 52.0 (OMe), 61.7 (*C*H_2OCO), 62.3 (C(3)), 87.9 (C(4)).

Reaction of the Bromomethoxy Adducts 5 and 6 with DBU in Benzene. A stirred solution of 5 (0.33 g, 0.55 mmol) in anhydrous benzene (8 mL) was cooled at 5 °C and then treated dropwise with a solution of DBU (1.22 g, 8.0 mmol) in anhydrous benzene (2 mL). The resulting mixture was stirred for 24 h at room temperature and then diluted with $CHCl_3$, washed (10% aqueous HCl, 10% aqueous $NaHCO_3$, brine), filtered, and evaporated. The oily residue (0.26 g) was subjected to preparative TLC, using 4:1 toluene–ethyl acetate as the eluent. Extraction with CH_2Cl_2 of the more intense band gave pure **3-methyl-4α-methoxy-4β-[[(*p*-nitrobenzoyl)oxy]methyl]-7β-(phenoxyacetamido)-2-cephem (9)** (0.062 g, 22%), as an oil: IR ($CHBr_3$) ν 1779 (β-lactam C=O), 1728 (ester C=O), 1693 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 1.89 (d, 3, J = 1.3 Hz, CCH_3), 3.33 (s, 3, OCH_3), 4.64 and 5.19 (2 d, 2, J = 11.8 Hz, CH_2OCO), 5.09 (d, 1, J = 4.7 Hz, CHS), 5.75 (dd, 1, J = 4.7 and 9.1 Hz, NHC*H*), 6.40 (d, 1, J = 1.3 Hz, C=CH), 8.18 (br s, 4, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{24}H_{23}N_3O_8S$: C, 56.13; H, 4.51; N, 8.18. Found: C, 56.22; H, 4.72; N, 7.98.

Treatment of a solution of 6 (0.12 g, 0.2 mmol) in anhydrous benzene (2.9 mL) with a solution of DBU (0.44 g, 2.9 mmol) in the same solvent (0.73 mL) under the conditions described for the preparation of 9 from 5 yielded, after the usual workup, the unchanged starting compound (6).

(4*R*,2′*R*)-3-Methyl-7β-(phenoxyacetamido)-4-spiro-4′-[2′-methoxy-2′-(*p*-nitrophenyl)-1′,3′-dioxolane]-2-cephem (10). A solution of 7 (0.16 g, 0.27 mmol) in anhydrous benzene was treated as described for the preparation of 9, with a solution of DBU (0.59 g, 3.87 mmol) in anhydrous benzene (0.96 mL). Preparative TLC of the crude product (0.13 g), eluting with 4:1 toluene–ethyl acetate, yielded pure 10 (0.042 g, 31%) as a vitreous product: IR ($CHBr_3$) ν 1777 (β-lactam C=O), 1690 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 1.65 (d, 3, J = 1.2 Hz, CCH_3), 3.25 (s, 3, OCH_3), 4.50 and 5.43 (2 d, 2, J = 9.0 Hz, $CH_2OC(O)_2C$), 5.13 (d, 1, J = 4.8 Hz, CHS), 5.75 (dd, 1, J = 4.8 and 9.0 Hz, NHC*H*), 6.16 (d, 1, J = 1.2 Hz, C=CH), 7.77 and 8.26 (AA′BB′ system, 4, J = 9.0 Hz, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{24}H_{23}N_3O_8S$: C, 56.13; H, 4.51; N, 8.18. Found: C, 56.28; H, 4.79; N, 7.87.

(4*R*,2′*S*)-3-Methyl-7β-(phenoxyacetamido)-4-spiro-4′-[2′-methoxy-2′-(*p*-nitrophenyl)-1′,3′-dioxolane]-2-cephem (11). A stirred solution of **8** (0.27 g, 0.45 mmol) in anhydrous benzene (5.3 mL) was treated as described for the preparation of **9**, with a solution of DBU (0.81 g, 5.3 mmol) in anhydrous benzene (1.3 mL). The crude product (0.22 g) was purified by preparative TLC using 4:1 toluene–ethyl acetate as the eluent to yield pure **11** as a vitreous product (0.086 g, 37%): IR ($CHBr_3$) ν 1783 (β-lactam C=O), 1693 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 2.06 (d, 3, J = 1.2 Hz, CCH_3), 3.31 (s, 3, OCH_3), 4.36 and 5.10 (2 d, 2, J = 9.1 Hz, $CH_2OC(O)_2C$), 4.88 (d, 1, J = 4.4 Hz, CHS), 5.31 (dd, 1, J = 4.4 and 9.3 Hz, NHC*H*), 6.29 (d, 1, J = 1.2 Hz, C=CH), 7.77 and 8.25 (AA′BB′ system, 4, J = 9.0 Hz, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{24}H_{23}N_3O_8S$: C, 56.13; H, 4.51; N, 8.18. Found: C, 56.18; H, 4.68; N, 8.02.

Thermal Transformation of the Orthoester 10. A solution of **10** (0.060 g) in anhydrous MeOH (10 mL) was refluxed for 24 h under nitrogen. After the mixture cooled, the solvent was evaporated to yield an oily residue (0.060 g) consisting almost exclusively of **9** (^1H NMR, TLC).

When **10** (0.040 g) was treated with MeOH-d_4 under the above-described conditions that lead from **10** to **9**, a vitreous product was obtained (0.040 g) consisting of practically pure **15**: ^1H NMR ($CDCl_3$) δ 1.89 (d, 3, J = 1.3 Hz, CCH_3), 4.64 and 5.19 (2 d, 2, J = 11.8 Hz, CH_2OCO), 5.09 (d, 1, J = 4.7 Hz, CHS), 5.75 (dd, 1, J = 4.7 and 9.1 Hz, NHC*H*), 6.40 (d, 1, J = 1.3 Hz, C=CH).

When the orthoester **11** was treated in refluxing MeOH, as described above for **10**, it was recovered unchanged (^1H NMR, TLC).

Reaction of the Orthoesters 7 and 8 with Silver Acetate in Acetic Acid. A solution of the orthoester (**7** or **8**) (0.46 g, 0.77 mmol) in glacial acetic acid (17.5 mL) was treated with silver acetate (0.22 g, 1.32 mmol) under the conditions previously used in the ring-contraction reactions of **5** and **6** to **13** and **14**, respectively.[2] The usual workup led to the recovery only of a complex mixture of decomposition products (IR, ^1H NMR, TLC).

Reaction of the Bromomethoxy Adducts 5 and 6 with Silver Acetate in Methanol. A solution of **5** (0.16 g, 0.27 mmol) in anhydrous methanol (12.5 mL) was added to silver acetate (0.23 g, 1.38 mmol), and the resulting suspension was heated at 60 °C with stirring. After 24 h at the same temperature, the solvent was evaporated and the residue was taken up with $CHCl_3$, filtered through Celite to remove silver salts, and evaporated to give a solid residue (0.14 g, 90%) consisting almost exclusively of the penam derivative **12**.[2]

When the bromomethoxy adduct **6** was treated with silver acetate in anhydrous MeOH under the conditions described above for **5**, it was recovered unchanged (^1H NMR, TLC).

Reaction of the Orthoester 7 with Silver Acetate in Anhydrous Methanol. A stirred suspension of **7** (0.17 g, 0.28 mmol) and silver acetate (0.24 g, 1.44 mmol) in anhydrous methanol (13 mL) was treated as described above for **5** to yield an oily residue (0.18 g) consisting of **10** and **9** in a ratio of about 2:1 (^1H NMR). Preparative TLC, eluting with 4:1 toluene–ethyl acetate, gave pure **10** (0.052 g, 36%) and **9** (0.020, 14%).

Reaction of the Orthoester 8 with Silver Acetate in Anhydrous Methanol. A solution of **8** (0.16 g, 0.27 mmol) in anhydrous methanol (12.5 mL) was treated with silver acetate (0.23 g, 1.38 mmol) under the conditions described above for the transformation of **5** into **12**. Removal of silver salts and evaporation of the organic solvent gave an oily residue (0.18 g) consisting of **11** and **(3*S*,2′*S*)-2α-(acetoxymethyl)-2-methyl-6β-(phenoxyacetamido)-3-spiro-4′-[2′-methoxy-2′-(*p*-nitrophenyl)-1′,3′-dioxolane]penam (14)** in a ratio of about 3:1 (^1H NMR). The crude product was subjected to preparative TLC, eluting with 4:1 toluene–ethyl acetate.

Extraction with $CHCl_3$ of the band with the higher R_f value gave pure **11** (0.075 g, 54%). Extraction with $CHCl_3$ of the band with the lower R_f yielded an oily residue consisting of pure **14** (0.033 g, 21%): IR ($CHBr_3$) ν 1789 (β-lactam C=O), 1748 (ester C=O), 1688 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 1.68 (s, 3, CCH_3), 2.06 (s, 3, $OCOCH_3$), 3.29 (s, 3, OCH_3), 3.76 and 4.40 (2 d, 2, J = 12.2 Hz, CH_2OCOCH_3), 4.22 and 5.21 (2 d, 2, J = 9.3 Hz, $CH_2OC(O)_2C$), 5.10 (d, 1, J = 4.2 Hz, CHS), 5.51 (dd, 1, J = 4.2 and 9.8 Hz, NHC*H*), 7.74 and 8.24 (AA′BB′ system, 4, J = 9.0 Hz, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{26}H_{27}N_3O_{10}S$: C, 54.44; H, 4.74; N, 7.33. Found: C, 54.58; H, 4.89; N, 7.28.

Crystallography. Crystals of **7**, mp 131–132.5 °C, were obtained by slow evaporation of an acetone solution containing hexane: $C_{24}H_{24}BrN_3O_8S$, M = 590.43, monoclinic, space group $C2$, a = 33.573 (3) Å, b = 7.377 (2) Å, c = 10.741 (2) Å, β = 96.59°, Z = 4, V = 2642.6 (9) Å^3, D_c = 1.494 g·cm^{-3}, $F(000)$ = 1216, λ(Cu K_α) = 1.541 78 Å, μ(Cu K_α) = 32.98 cm^{-1}.

Cell parameters and orientation matrix were obtained by least-squares refinement using 28 reflections in the range $20 < \theta < 35°$ and Cu K_α radiation. A transparent prism of 0.14 × 0.08 × 0.50 mm was used to collect data at room temperature on a Siemens AED diffractometer[14] using $\theta/2\theta$ scan mode, scan speed 3–12° min^{-1}, scan width (1.20 + 0.14 tan θ), and θ in the range 3–70°. One standard reflection was measured every 100. A total of 2717 intensities were corrected for Lorentz and polarization, but not for absorption; 2147 with $I/\sigma(I) \geq 3$ were used to solve the structure with the SHELX-86 program.[15] All the calculations were performed on the Gould computer system of the Centro di Strutturistica Diffrattometrica del CNR, Parma. The refinement (anisotropic for the heavy atoms and rigid-body constraint for the two phenyl rings, isotropic for the hydrogens put in calculated positions) was performed by full-matrix least-squares using the program SHELX-76[16] with the form factors there included; the final indexes were R = 0.0340 and R_w = 0.0379 ($w = 0.1399/[\sigma^2(F) + 0.011F^2]$). Figure 1 was obtained with use of an ORTEP program.[17]

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Supplementary Material Available: Table II giving selected bond distances, bond angles, and torsion angles and Table III giving final atomic coordinates and isotropic B equivalents (2 pages); observed and calculated structure factor amplitudes (13 pages). Ordering information is given on any current masthead page.

(14) Belletti, D.; Ugozzoli, F.; Cantoni, A.; Pasquinelli, G. Gestione on line di diffrattometro a cristallo singolo SIEMENS AED con sistema General Automation Jumbo 220, Internal Reports 1-3, 1979.

(15) Sheldrick, G. M. *SHELX-86. Program for Crystal Structure Solution*; University of Gottingen: Gottingen, Federal Republic of Germany, 1986.

(16) Sheldrick, G. M. *SHELX-76. Program for Crystal Structure Determination*; University of Cambridge: Cambridge, England, 1976.

(17) Johnson, C. K. *ORTEP II, Fortran Thermal Ellipsoids Plot Program for Crystal Structure Illustration*; Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.