References and Notes

(1) D. Redmore, *J. Org. Chem.*, **35**, 4114 (1970).
(2) D. Redmore, *J. Org. Chem.*, **38**, 1306 (1973).
(3) The position of attack by cyanide ion on *N*-alkoxypyridinium salts can be C-4 or C-2 depending on reaction conditions. See, A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, New York, N.Y., 1971.
(4) R. E. Lyle and C. B. Boyce, *J. Org. Chem.*, **39**, 3708 (1974).
(5) The isopropoxy groups show nonequivalent methyl groups; see T. H. Siddall and C. A. Prohaska, *J. Am. Chem. Soc.*, **84**, 3467 (1962), and L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance in Organic Chemistry", Pergamon Press, Oxford, 1969, pp 368–379.
(6) The C–P coupling constants are consistent with the assignments; see J-R. Llinas, E-J. Vincent, and G. Peiffer, *Bull. Soc. Chim. Fr.*, 3209 (1973).
(7) These analytical data are more consistent with a hemihydrate structure; the hygroscopic nature of pyridylphosphonates was noted earlier (ref 1).

Chemistry of the Dihydrothiazine Ring Moiety of Cephalosporins. 1. Regiospecificity and Stereoselectivity in the Bromine Addition to 2-Cephem Derivatives. A New Route to 2-Methoxy Cephalosporins

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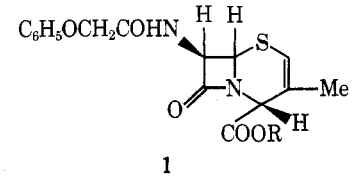
The reactions of Δ^2-deacetoxycephalosporin (**1a**) with Br_2 in aprotic solvents (CCl_4 and CH_2Cl_2) yielded mixtures of the diastereoisomeric 2,3-dibromides **2a** and **3a**. The same reaction in MeOH afforded a mixture of the 2-methoxy-3-bromo derivatives **4a** and **5a**, whereas in 2-PrOH it gave exclusively **2a** and **3a**. **2a** and **3a** were transformed respectively to **4a** and **5a** with practically complete retention of configuration by treatment with MeOH in the presence of $Me_2NC_6H_5$. **4a** and **5a** were dehydrohalogenated to the corresponding 2-methoxy cephalosporin derivatives **6a** and **7a**. Compounds **6b** and **7b** were prepared through a similar sequence. **6** and **7** were transformed into the acids **6** (R = H) and **7** (R = H). The configurations of the substituents at C_2 and C_3 were demonstrated through chemical transformations and from their NMR spectra by NOE experiments. The stereochemical results and the mechanisms of the reactions are discussed.

The 2- or 3-cephem double bond may be a good point of attack for the introduction of new substituents into the dihydrothiazine ring of cephalosporins. Whereas the 3-cephem double bond appears to be very unreactive toward electrophilic reagents,[1] the 2-cephem one appeared to us more susceptible to attack by such agents because of the more favorable electronic effects of the substituents on the double bond. We wish to report the addition of Br_2 to Δ^2-deacetoxycephalosporins **1** and some reactions of the bromine addition products. In addition to the pharmaceutical purpose, this research represents, to our knowledge, the first approach to the study of the stereochemical aspect of the electrophilic addition to the double bond of a vinyl thioether. The mechanism of the bromination reactions of the olefinic double bond,[2] as well as that of the analogous reactions of vinyl ethers,[3] has been extensively studied. It may be stressed, however, that the steric course of this type of reactions is strongly depending on the steric and electronic effects of the double bond substituents and on the reaction conditions[2-4] and, therefore, in several cases not simply predictable.



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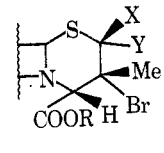
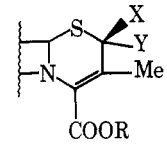


A



B

2, X = Br; Y = H
3, X = H; Y = Br
4, X = OMe; Y = H
5, X = H; Y = OMe

6, X = OMe; Y = H
7, X = H; Y = OMe

a, R = *p*-$MeOC_6H_4CH_2$
b, R = *p*-$NO_2C_6H_4CH_2$

Results

The treatment of a solution of **1a**[5] in CCl_4 or CH_2Cl_2 with a dilute solution of Br_2 in the same solvent afforded mixtures of the two diastereoisomeric dibromides **2a** and **3a**. The ratio between **2a** and **3a** changes with the solvent, the trans dibromide (**2a**) being predominant in CCl_4 and the cis dibromide (**3a**) in CH_2Cl_2 (Table I). The reaction of these mixtures with MeOH in presence of $Me_2NC_6H_5$ yielded in nearly quantitative yield mixtures of the 2-methoxy derivatives **4a** and **5a** with practically complete retention of configuration. A 25:75 mixture of **4a** and **5a** was directly obtained from **1a** by treatment with Br_2 in MeOH. On the contrary, bromination of **1a** in 2-PrOH gave a mixture of **2a** and **3a** (Table I); no trace of alkoxybromo derivatives was revealed. Dehydrohalogenation of **4a** and **5a** with Et_3N in benzene at room temperature gave the corresponding Δ^3 derivatives **6a** and **7a**, which have been separated by preparative TLC. Esters **6b** and **7b** were prepared through a similar sequence. Both **2** and **3**, and **4** and **5** refused to crystallize and separation attempts by chromatography led to extensive decomposition and dehydrobromination to **6** and **7**, respectively; their crude mixtures were, therefore, used directly for subsequent transformations. Compounds **2**, **3**, **4**, and **5** were, however, stable under the reaction conditions. Hydrogenolysis of **6b** and **7b** on Pd/C and cleavage of **6a** with CF_3COOH in benzene in the presence of

Table I. Stereochemical Results of the Bromination Reactions of 1a and of the Subsequent Transformations of the Bromine Addition Products

Solvent	Temp, °C	Bromine addition products		Methanolysis products		Dehydrobromination products	
		% **2a**	% **3a**	% **4a**	% **5a**	% **6a**	% **7a**
CCl_4	0	56	44	60	40	58	42
CCl_4	−16	58	42	62	38	64	36
CH_2Cl_2	0	27	73	24	76	23	77
CH_2Cl_2	−75	23	77	25	75	20	80
2-PrOH	0	83	17				

Table II. ^{1}H NMR Data of Saturated and Δ^3-Cephalosporins

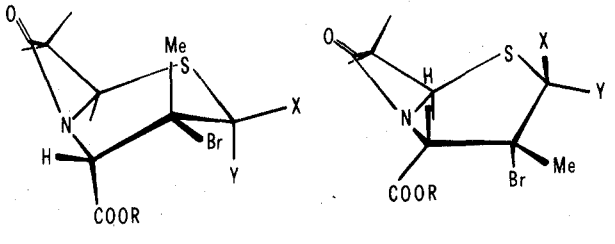
Compd	2-OMe	H-2	3-Me	H-4	H-6	H-7	OCH_2CO	R	
								OCH_2	OMe
2a		5.40 s	2.14 s	4.90 s	5.57 d	5.69 q	4.53 bs	5.16 bs	3.79 s
2b		5.37 s	2.09 s	4.87 s	5.58 d	5.73 q	4.54 bs	5.20 bs	
3a		5.37 s	2.23 s	4.92 s	5.50 d	5.77 q	4.53 bs	5.12 bs	3.77 s
3b		5.32 s	2.12 s	4.91 s	5.52 d	5.80 q	4.54 bs	5.15 bs	
4a	3.42 s	5.08 s	2.06 s	4.77 s	5.15 d	5.62 q	4.52 s	5.16 bs	3.81 s
4b	3.38 s	5.28 s	2.09 s	4.84 s	5.20 d	5.66 q	4.50 s	5.26 bs	
5a	3.29 s	5.06 s	2.10 s	4.82 s	5.33 d	5.67 q	4.55 s	5.08 bs	3.81 s
5b	3.34 s	5.25 s	2.12 s	4.87 s	5.28 d	5.70 q	4.54 bs	5.24 bs	
6a	3.31 s	4.64 s	2.36 s		5.19 d	5.73 q	4.50 s	5.18 s	3.79 s
6b	3.35 s	4.70 s	2.35 s		5.25 d	5.79 q	4.52 s	5.20 s	
7a	3.41 s	4.75 s	2.13 s		5.03 d	5.88 q	4.54 s	5.20 s	3.78 s
7b	3.47 s	4.82 s	2.19 s		5.11 d	5.95 q	4.58 s	5.23 s	

anisole yielded the corresponding 2-alkoxy cephalosporanic acids **6** (R = H) and **7** (R = H).[6]

The structure of all compounds have been determined on the basis of their ^{1}H NMR spectra; the main spectral parameters are shown in Table II. The proton magnetic resonance assignments have been firmly established on the basis of the area, of the expected chemical shift, and of the multiplicity of the signal.[7]

Discussion

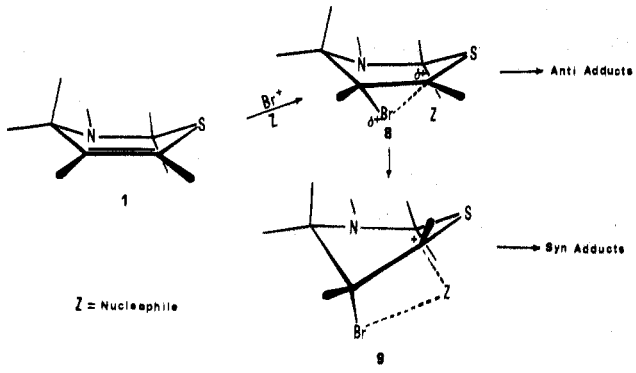
The trans relationship between the 3-Br and the H-4β in both derivatives **4** and **5** and therefore in both the dibromides **2** and **3** results from the easy dehydrobromination[8] of **4** and **5**. The study of the internal nuclear Overhauser effect (NOE)[7] between 3β-Me and H-2 and H-4 in **2a** and **3a** confirmed the configuration of the substituents at C-2 in the dibromides and gave some evidence for the tetrahydrothiazine ring conformation in these compounds. Only the 2β,3α isomer in the half-chair conformation A is in accordance with the presence of an relatively strong NOE between 3β-Me and H-4β (15.5%) and with the absence of an NOE between 3β-Me and H-2, as observed for **2a**. The occurrence of an NOE between 3β-Me and both H-2 (19.0%) and H-4β (15.0%) in **3a** can be accounted by the 2α,3α isomer in both the conformations A and B;



A B

however, the absence of a W long-range coupling constant between H-2 and H-4, which should be present in A,[9] speaks in favor of the half-boat conformation B. The relief of the diaxial interactions between 3β-Me and the lactam ring, and the 2α substituent and the 4α-carboxy group which would be present in the half-chair conformation A may account for the existence of **3a** in the usually unfavorable half-boat conformation. The configurations at C-2 in the 2-methoxy-3-bromo derivatives **4** and **5** were proven by converting them into the corresponding unsaturated esters **6** and **7** and finally into the acids **6** (R = H) and **7** (R = H). The presence of an NOE between 3-Me and H-2 (17–20%) and of a long-range ^5J coupling constant (0.5 Hz) between H-2 and H-7α in **7a** and the lack of such effects in **6a** firmly indicate the respective configurations of the substituents on C-2. On the other hand, **7b** was found to be identical with a sample of the same product prepared according to Spry.[6]

The electrophilic step of the addition to an olefinic double bond in reactions initiated by positive bromine[2] can lead to a symmetrical or unsymmetrical bridged bromonium ion and to an open bromocarbenium ion,[10] depending on the nature of the double bond and the reaction conditions. The exclusive formation of the 2-methoxy-3α-bromo derivatives **4a** and **5a** in the reaction of **1a** with Br_2 in MeOH shows that the attack of positive bromine occurs from the α side and that the subsequent nucleophilic attack takes place on the carbon adjacent to sulfur. An analogous trend can be also rationally assumed for the bromination reactions of **1**. The preferential attack of the positive bromine from the α side of the dihydrothiazine ring in these reactions may be rationalized on the basis of the preferred conformation of the Δ^2-cephem derivatives,[11] through a shielding by the lactamic ring and by the pseudoaxial H-4β toward an approach of the reagent from the β side. An analogous selectivity has been previously observed in the catalytic hydrogenation of a Δ^2-cephem derivative.[12] The complete regiospecificity of the nucleophilic step in both the formation of syn and anti derivatives should imply intermediates, such as **8** or **9**, with a high degree of carbocation character on the carbon adjacent to sulfur because of the resonance electron donation by sulfur.[13] Also the lack of a clear anti stereoselectivity in the nucleophilic step is in accordance with a similar mechanism. Whereas the anti products (**2** and **4**) must arise from a nucleophilic attack on the intermediate **8** in which the Br–C bond is not completely broken,[14] the syn products (**3** and **5**) should derive from the open ion **9** through



the collapse of an ion pair or an ion–nucleophile pair in which the cation (**9**) and the counterion or the nucleophile are held together probably by electrostatic interactions.[2,4,14,15] The mechanistic scheme proposed is supported by the presence of both the syn and the anti adduct in the Br_2 addition to Δ^2-dihydrothiapyran, selected by us as a simple model for the addition reactions to the Δ^2-cephem system.[16] Analogous stereochemical results were also obtained in the halogenation reactions of Δ^2-dihydropyran.[3] The different course of the bromination reactions of **1a** conducted in MeOH and in 2-PrOH must be attributed to the steric difference between the two alcohols. This effect, enhanced by the concurrent high steric hindrance of the substrate, can cause the exclusive attack of the bromide ion in the reaction in 2-PrOH notwithstanding its low relative concentration. Finally, the facile and exclusive substitution of the bromine on C-2 in the methanolysis of **2** and **3** is in accordance with the high reactivity of α-halo sulfide toward nucleophilic substitution reactions.[17] The retention of configuration observed can be rationalized through a SNi-type substitution[18,19] of the pseudoequatorial bromine in both **2** and **3**.

Both 2α-methoxy (**7**, R = H)[6] and 2β-methoxy cephalosporin derivative (**6**, R = H) showed similar antibacterial activity only against gram-positive bacteria.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. Ir spectra were taken on paraffin oil mulls on a Perkin-Elmer Infracord Model 137. The uv spectra were measured in methanol solution. NMR spectra were performed on a Varian 100-MHz, Model HA in solution of $CDCl_3$. Chemical shifts (δ, ppm), referenced to Me_4Si as an internal standard, are believed to be accurate to ±0.01 ppm. The relative percentages of compounds **2** and **3**, **4** and **5**, and **6** and **7** have been calculated on the basis of the integrals of the 3-Me singlets on the NMR spectra of the crude reaction products. Preparative TLC was performed on 2-mm layer silica gel plates (Merck F_{254}) containing a fluorescent indicator; spots were detected under uv light (245 nm). All comparisons between compounds were made on the basis of their NMR spectra and their melting points. Evaporations were made in vacuo (rotating evaporator). CCl_4 and CH_2Cl_2 were refluxed over P_2O_5 and rectified.

***p*-Methoxybenzyl (1a) and *p*-nitrobenzyl 3-methyl-7-(phenoxyacetamido)-2-cephem-4-carboxylate (1b)** were prepared as previously described:[5] **1a**, mp 111–113 °C (lit.[5] mp 112–114 °C); **1b**, mp 130–132 °C (lit.[5] mp 130 °C).

Reaction of 1a with Bromine in Anhydrous CCl_4. A solution of **1a** (3.0 g, 6.4 mmol) in anhydrous CCl_4 under N_2 was treated dropwise under stirring with a solution of bromine (2.05 g, 12.8 mmol) in the same solvent (50 ml) at the chosen temperature. When the addition was complete, the reaction mixture was left at the same temperature for 10 min and then washed (0.1 N aqueous $Na_2S_2O_3$ and H_2O) and evaporated to yield a viscous oil (3.75 g) consisting of **2a** and **3a**, which was analyzed by NMR (see Table I). The residue refused to crystallize. Separation attempts of the mixture of **2a** and **3a** by chromatography led to extensive decomposition. Their crude mixture was directly used for subsequent transformation. Compounds **2a** and **3a** were stable under the reaction conditions. Anal. Calcd for $C_{24}H_{24}Br_2N_2O_6S$: C, 45.88; H, 3.85; N, 4.46; Br, 25.43. Found: C, 45.52; H, 3.75; N, 4.36; Br, 25.02.

Reaction of 1a with Bromine in Anhydrous CH_2Cl_2. A solution of **1a** (4.0 g, 8.5 mmol) in anhydrous CH_2Cl_2 was treated, as described above for the reaction in CCl_4, with a solution of bromine (2.70 g, 17.0 mmol) in CH_2Cl_2 yielding a crude gummy product (4.45 g) consisting of **2a** and **3a** (NMR) (see Table I), which did not crystallize. Also in this case purification attempts of the reaction mixture were unsuccessful and crude mixture was used in the following reactions. **2a** and **3a** were stable under the reaction conditions. Anal. Calcd for $C_{24}H_{24}Br_2N_2O_6S$: C, 45.88; H, 3.85; N, 4.46; Br, 25.43. Found: C, 45.48; H, 3.70; N, 4.30; Br, 25.06.

Reaction of 1a with Bromine in Anhydrous Methanol. A solution of **1a** (0.200 g, 0.43 mmol) in anhydrous methanol (100 ml) was treated under N_2 with $CaCO_3$ powder (0.400 g) and the resulting stirred suspension was added dropwise at 0 °C with a solution of bromine (0.137 g, 0.86 mmol) in anhydrous methanol (30 ml). When the addition was complete the reaction mixture was left for 15 min at 0 °C and then evaporated. The residue was dissolved in CH_2Cl_2, washed (0.1 N aqueous $Na_2S_2O_3$ and H_2O), and evaporated to yield a mixture of **4a** and **5a** (0.228 g), as a yellow glue, which was identified spectrally. No trace of the dibromides **2a** and **3a** was revealed.

Reaction of 1a with Bromine in Anhydrous 2-Propanol. A stirred solution of **1a** (0.200 g, 0.43 mmol) in anhydrous 2-propanol (100 ml) was cooled at 0 °C and treated dropwise in the presence of $CaCO_3$ (0.400 g) with a solution of bromine (0.137 g, 0.86 mmol) in the same solvent (30 ml). After 15 min at 0 °C a further amount of bromine (0.274 g, 1.72 mmol) in anhydrous 2-propanol (60 ml) was added. When the addition was complete the reaction mixture was left at 0 °C for 1 h and then evaporated. The residue was dissolved in CH_2Cl_2, washed (0.1 N aqueous $Na_2S_2O_3$ and H_2O), and evaporated, yielding a gummy mixture of **2a** and **3a** (0.240 g) which was analyzed by NMR (see Table I). No trace of alkoxy bromo derivatives was revealed. The mixture was stable under the reaction conditions, but decomposed when subjected to chromatography.

Methanolysis of the Mixtures of the Dibromides 2a and 3a. A. Dibromides Obtained in CCl_4. A solution of the crude mixture of **2a** and **3a** (3.75 g, 6.0 mmol), obtained from the bromination reaction of **1a** in CCl_4 at 0 °C in anhydrous methanol (400 ml), was added with $Me_2NC_6H_5$ (2.55 g, 21.0 mmol), left for 6 days at room temperature, and evaporated to dryness. The residue was dissolved in CH_2Cl_2, washed in succession with 3% aqueous HCl, H_2O, 5% aqueous $NaHCO_3$, and H_2O, and evaporated to yield a gummy product (2.6 g) consisting of **4a** and **5a** which was directly analyzed through NMR (see Table I). The mixture did not crystallize and attempts to separate it by chromatography led to extensive dehydrobromination to **6a** and **7a**, and it was directly used in the following transformation. Compounds **4a** and **5a** were, however, stable under the reaction conditions. Anal. Calcd for $C_{25}H_{27}BrN_2O_7S$: C, 51.82; H, 4.70; N, 4.83; Br, 13.80. Found: C, 51.22; H, 4.48; N, 4.56; Br, 13.35.

Analogous treatment of the mixture of **2a** and **3a**, obtained from the bromination of **1a** in CCl_4 at −16 °C, afforded a mixture of **4a** and **5a** in the ratio reported in Table I.

B. Dibromides Obtained in CH_2Cl_2. A solution of the mixture of **2a** and **3a** (4.35 g), obtained in the bromination of **1a** in CH_2Cl_2 at 0 °C in anhydrous methanol (470 ml) was treated with $Me_2NC_6H_5$ as described above in A to yield a mixture of **4a** and **5a** (3.85 g), which was identified spectrally (NMR) (see Table I) and used directly in the subsequent reaction. Also in this case the product was not crystalline and dehydrohalogenated to **6a** and **7a** when it was subjected to chromatography, but it was stable to the reaction conditions. Anal. Calcd for $C_{25}H_{27}BrN_2O_7S$: C, 51.82; H, 4.70; N, 4.83; Br, 13.80. Found: C, 51.21; H, 4.44; N, 4.40; Br, 13.40.

When the mixture of **2a** and **3a**, formed in the bromination of **1a** in CH_2Cl_2 at −75 °C, was subjected to the same treatment the results reported in Table I were obtained.

Dehydrobromination of the Mixtures of 4a and 5a. $N(C_2H_5)_3$ (1.40 g, 13.8 mmol) was added to a stirred solution of a mixture of **4a** and **5a** (4.0 g, 6.9 mmol) in anhydrous benzene (300 ml). After stirring for 36 h at room temperature the reaction mixture was washed (successively with 3% aqueous HCl, H_2O, 5% aqueous $NaHCO_3$, and H_2O). Evaporation of the solvent yielded a residue consisting of a mixture of **6a** and **7a** (3.25 g) which was analyzed by NMR.

An attempt to dehydrobrominate a mixture of dibromides **2a** and **3a** using conditions described above was unsuccessful owing to extensive decomposition. The brown gummy residue obtained did not show the β-lactamic resonance in the NMR spectra.

***p*-Methoxybenzyl 2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate (7a).** A 23/77 mixture of **6a** and **7a** prepared through the sequence described above from the dibromides mixture obtained in the bromination of **1a** in CH_2Cl_2 at 0 °C was crystallized twice from acetone–hexane to yield pure **7a** (1.41

g), mp 161.5–162 °C. Anal. Calcd for $C_{25}H_{26}N_2O_7S$: C, 60.24; H, 5.26; N, 5.62; S, 6.43. Found: C, 59.92; H, 5.21; N, 5.58; S, 6.56.

p-Methoxybenzyl 2β-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate (6a). A 58/42 mixture of **6a** and **7a** (0.500 g), prepared through the sequence described above from the mixture of **2a** and **3a** obtained in the bromination of **1a** in CCl_4 at 0 °C, was subjected to preparative TLC, a 7:3 mixture of ethyl acetate and hexane being used as the eluent. Elution was repeated three times. Extraction of the two bands (the faster moving band contains **7a**) yielded **7a** (0.070 g), mp 161.5–162 °C, and pure **6a** as an oil (0.110 g). Anal. Calcd for $C_{25}H_{26}N_2O_7S$: C, 60.24; H, 5.26; N, 5.62; S, 6.43. Found: C, 59.90; H, 5.18; N, 5.30; S, 6.33.

p-Nitrobenzyl 2β-Methoxy- (6b) and p-Nitrobenzyl 2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate (7b). A mixture of **2b** and **3b** (2.50 g) obtained from the bromination of **1b** (2.0 g) in CH_2Cl_2 at 0 °C as described above for **1a** was transformed into a mixture of **4b** and **5b** (2.05 g) and then into a mixture of **6b** and **7b** (1.45 g) through a sequence similar to that used above for the transformation of **2a** and **3a** into **6a** and **7a**. Two crystallizations of the crude mixture of **6b** and **7b** from acetone–hexane gave pure **7b** (0.300 g), mp 172–173 °C, identical with a sample prepared according to the method of Spry[6] (lit.[6] mp 171.5–172 °C). The mother liquors were subjected to TLC on silica gel, using a 7:3 mixture of ethyl acetate and hexane as the eluent. Elution was repeated twice. Extraction of the two bands (the faster moving band contains **7b**) yielded **7b** (0.110 g), mp 172–173 °C, and pure **6b** (0.220 g), as an oil. Anal. Calcd for $C_{24}H_{23}N_3O_8S$: C, 56.13; H, 4.51; S, 6.24. Found: C, 56.51; H, 4.45; S, 6.11.

2β-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylic Acid (6, R = H). A. A solution of **6a** (0.510 g) and anisole (0.36 ml) in anhydrous benzene (45 ml) was treated with trifluoroacetic acid (1.71 ml). After stirring for 2 h at room temperature the reaction mixture was evaporated, taken up in ethyl acetate, and extracted three times with 3% aqueous $NaHCO_3$. The aqueous extracts were washed with ethyl acetate, then layered with ethyl acetate and acidified to pH 3. Evaporation of the organic solvent gave a residue consisting of **6** (R = H) (0.250 g), which crystallized from 2-propanol to yield pure **6** (R = H) (0.090 g): mp 140–141 °C; uv λ_{max} 269 nm (ε 4650). Anal. Calcd for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40; S, 8.47. Found: C, 53.96; H, 4.86; N, 7.14; S, 8.43.

B. A suspension of **6b** (0.500 g) in a mixture of methanol (25 ml) and water (6 ml) was shaken under hydrogen at room temperature for 4 h in the presence of 5% Pd on carbon (0.150 g). The catalyst was then separated by filtration and the solvent evaporated. The residue was dissolved in ethyl acetate and extracted three times with 5% aqueous $NaHCO_3$. The aqueous extracts were washed with ethyl acetate, then layered with ethyl acetate, and acidified at pH 3. Evaporation of the organic solvent afforded an oil (0.220 g) which crystallized from 2-propanol to yield pure **6** (R = H) (0.110 g), mp 140–141 °C.

2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylic Acid (7, R = H). A suspension of **7b** (0.300 g) in methanol (20 ml) and water (4 ml) was hydrogenated as described above for the preparation of **6**, R = H, in B. Workup yielded crude **7**, R = H (0.120 g), as an oil which crystallized from acetone–hexane to give pure **7**, R = H (0.075 g), mp 141–145 °C. Anal. Calcd for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40; S, 8.47. Found: C, 53.65; H, 4.48; N, 7.38; S, 8.52. Spry[6] reports the formation of **7**, R = H, from **7b**, but no experimental value has been given.

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Registry No.—**1a**, 58800-52-5; **1b**, 24647-43-6; **2a**, 58747-39-0; **2b**, 58747-40-3; **3a**, 58747-41-4; **3b**, 58747-42-5; **4a**, 58747-43-6; **4b**, 58747-44-7; **5a**, 58747-45-8; **5b**, 58747-46-9; **6a**, 58747-47-0; **6b**, 58800-53-6; **6** (R = H), 58800-54-7; **7a**, 58747-48-1; **7b**, 37901-26-1; **7** (R = H), 58800-55-8.

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On the Role of Electronic and Steric Factors upon the Formation of Meisenheimer-Type Adducts

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The rate and equilibrium constants for the formation of Meisenheimer adducts from 4-cyano-2-nitrothiophene, 3-cyano-2-methoxy-5-nitrothiophene, and 5-cyano-2-methoxy-3-nitrothiophene have been determined in methanol at 25 °C. The comparison of these data with those for the formation of adducts from dinitrothiophene, trinitrobenzene, and cyanodinitrobenzene derivatives provides a reliable indication of the role of steric and electronic factors on the formation of the adducts.

A major factor in the formation of Meisenheimer adducts is the electron delocalization ability of electron-withdrawing substituents. However, other factors may more subtly modify the stability and the rate of formation of these adducts. In the reaction of 2,4,6-trinitroanisole (TNA) with methoxide ion in methanol solution the equilibrium is more shifted toward