

Chemistry of Cephalosporin Antibiotics.
 XVIII. Synthesis of
 7-Acyl-3-methyl-2-cephem-4-carboxylic
 Acid Esters

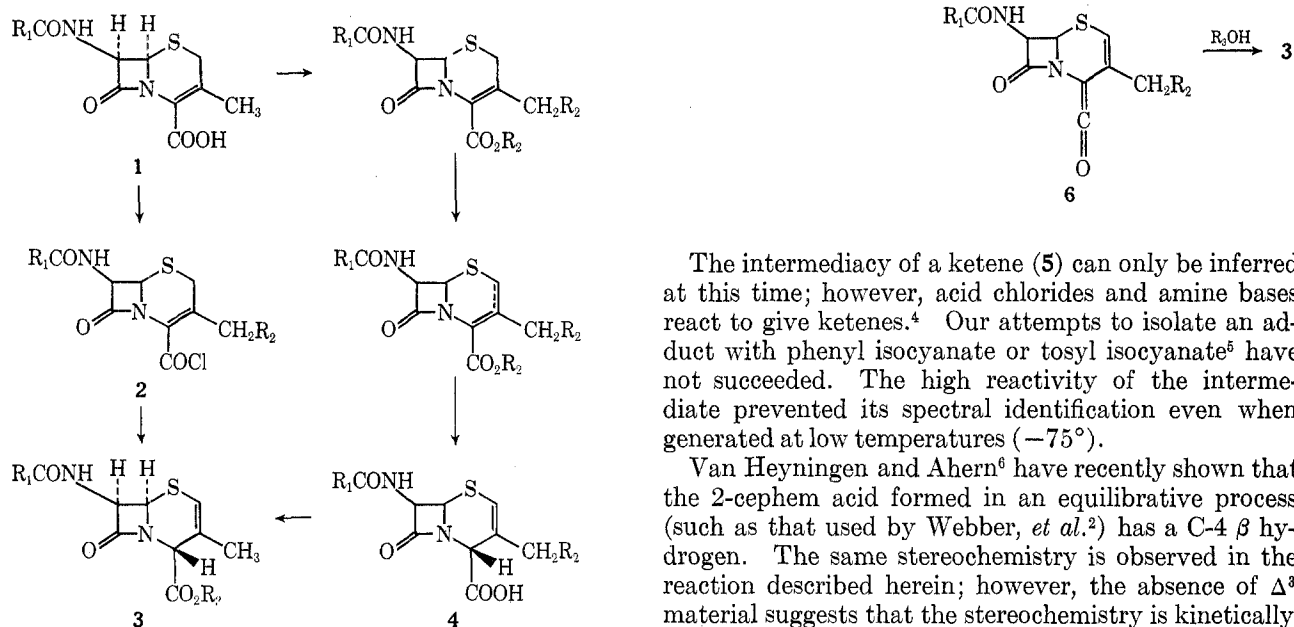
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Recent publications^{1,2} from these laboratories have described results which constitute the synthesis of a cephalosporin from a penicillin. In this and the following note,³ we report additional studies of the functionalization of deacetoxyethyl cephalosporins.²

The initial part of the Webber, *et al.*,² sequence involves an esterification of the 3-cephem acid **1**, an isomerization, and deesterification to give the 2-cephem acid **4**, which in turn is esterified to give an easily cleavable ester in low overall yield. An alternative preparation of pure 2-cephem esters involving the acid chloride **2** and a probable ketene intermediate is described herein.

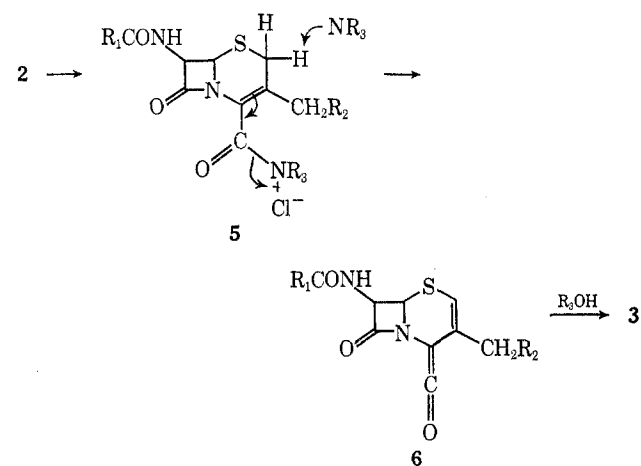


Δ^3 -Cephalosporanyl chlorides are best prepared in an inert solvent with oxalyl chloride, using *N,N*-dimethylformamide as a catalyst. Other acid chloride forming reagents, such as thionyl chloride or phosphorus pentachloride, with or without catalysts, are less effective.

The esterification conditions are dependent upon the nature of the alcohol being employed. Tertiary alcohols may be used in excess at ice-bath temperatures;

however, primary or secondary alcohols are used preferably in approximately equivalent amounts and at lower temperatures to minimize Δ^3 -ester formation. The reaction conditions require that the preformed acid chloride be added slowly to a solution of the alcohol and tertiary amine base in an inert solvent. Some of the esters prepared by this method are listed in Table I. The reaction is limited only by the stability and/or acidity of the alcohol and is readily adaptable to large scale (1 mol) preparations.

The mechanism of the esterification probably involves initial acylation of the tertiary amine. Another molecule of base then removes a proton at C-2, causing a double-bond shift ($\Delta^3 \rightarrow \Delta^2$) and expulsion of the tertiary amine group to give the very reactive ketene (**5** \rightarrow **6**). The ketene immediately reacts with the alcohol to give the 2-cephem ester (**6** \rightarrow **3**).



The intermediacy of a ketene (**5**) can only be inferred at this time; however, acid chlorides and amine bases react to give ketenes.⁴ Our attempts to isolate an adduct with phenyl isocyanate or tosyl isocyanate⁵ have not succeeded. The high reactivity of the intermediate prevented its spectral identification even when generated at low temperatures (-75°).

Van Heyningen and Ahern⁶ have recently shown that the 2-cephem acid formed in an equilibrative process (such as that used by Webber, *et al.*)² has a C-4 β hydrogen. The same stereochemistry is observed in the reaction described herein; however, the absence of Δ^3 material suggests that the stereochemistry is kinetically controlled. This may be explained by the α -face departure of the tertiary amine base preventing the attack of an alcohol molecule from that side. The alcohol, which may be held in position by a hydrogen bond to the amido hydrogen, would thus add to the β side of the ketene and give the observed stereochemical result.

Experimental Section

Melting points were determined on a Kofler melting point apparatus. Infrared spectra were determined on a Perkin-Elmer

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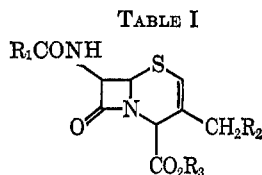
(2) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *ibid.*, **91**, 5674 (1969).

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(4) (a) T. Ozeki and M. Kusaka, *Bull. Chem. Soc. Jap.*, **39**, 1995 (1966); (b) T. Ozeki and M. Kusaka, *ibid.*, **40**, 1232 (1967); (c) G. B. Payne, *J. Org. Chem.*, **31**, 718 (1966); (d) W. E. Truce and P. S. Bailey, Jr., *ibid.*, **34**, 1341 (1969).

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Compd ^a	Registry no.	Empirical formula	Mp, °C	% yield	Reaction conditions	Calcd, %			Found, %		
						C	H	N	C	H	N
1	24647-38-9	C ₂₀ H ₂₄ N ₂ O ₆ S	78-80	87	A	59.20	5.98	6.93	59.20	6.08	6.63
2	24144-88-5	C ₂₄ H ₂₄ N ₂ O ₆ S	112-114	90	B	61.52	5.16	5.97	61.95	5.33	6.12
3	24647-40-3	C ₂₁ H ₂₂ N ₂ O ₆ S	92-93	85	A	60.86	5.35	6.76	61.02	5.59	7.00
4	24647-41-4	C ₂₁ H ₂₄ N ₂ O ₆ S	83-85	46	A	60.56	5.81	6.73	60.34	6.01	6.91
5	24647-42-5	C ₂₄ H ₂₂ N ₂ O ₆ S	145-146	77	B	61.80	4.75	6.01	62.06	4.97	6.14
6	24647-43-6	C ₂₃ H ₂₁ N ₂ O ₇ S	130	60	B	57.25	4.18	8.70	57.10	4.47	8.45
7	24647-44-7	C ₂₀ H ₂₀ N ₂ O ₆ S	110	45	B	67.69	5.09	5.45	67.82	5.18	5.59
8	24647-45-8	C ₂₀ H ₂₄ N ₂ O ₄ S	130-131	45	B	61.84	6.23	7.21	61.59	6.23	7.04
9	24647-46-9	C ₂₀ H ₂₄ N ₂ O ₆ S ₂	178	33	A	53.09	5.35	6.19	53.08	5.33	6.11

^a 1, R₁ = PhOCH₂; R₂ = H; R₃ = C(CH₃)₃. 2, R₁ = PhOCH₂; R₂ = H; R₃ = -CH₂--OCH₃. 3, R₁ = PhOCH₂; R₂ = H; R₃ = -C(C≡CH)(CH₃)₂. 4, R₁ = PhOCH₂; R₂ = H; R₃ = -C(CH=CH₂)(CH₃)₂. 5, R₁ = PhOCH₂; R₂ = H; R₃ = CH₂C(=O)Ph. 6, R₁ = PhOCH₂; R₂ = H; R₃ = CH₂--NO₂. 7, R₁ = PhOCH₂; R₂ = H; R₃ = -CH(Ph)₂. 8, R₁ = PhCH₂; R₂ = H; R₃ = C(CH₃)₃. 9, R₁ = ; R₂ = OAc; R₃ = C(CH₃)₃.

Model 21 in a KBr disk. The ultraviolet spectra were measured in methanol solution. The nmr spectra were recorded with Varian Models A-60 and HA-60 spectrometers at 60 MHz in 5-10% deuteriochloroform solution with tetramethylsilane as an internal standard. Elemental analyses were determined by our microanalytical laboratory.

3-Methyl-7-phenoxyacetamido-3-cephem-4-carbonyl Chloride.—A suspension of 0.353 g (1.02 mmol) of 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid in 40 ml of C₆H₆ was cooled in ice and stirred while 0.256 g (2 mmol) of oxalyl chloride and 1 drop of DMF were added. The reaction mixture was stirred at about (7-10°) for 45 min, and then the solvents were removed under reduced pressure. An nmr spectrum of the acid chloride showed the absence of any 2-cephem isomer.

The acid chloride (~200 mg) was dissolved in 10 ml of MeOH and stirred at 25° for 30 min. The solvent was removed, and the residue was redissolved in C₆H₆. The C₆H₆ solution was washed with H₂O, 3% HCl, and 10% NaHCO₃. The solution was dried over Na₂SO₄ and evaporated to dryness to give 0.160 g of methyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate. The ester was crystallized from EtOAc and was found to be identical with authentic material¹ by tlc, mp 135-137°, mmp 135-138°.

The acid chloride as prepared above was used in the following preparations. These preparations are presented as typical examples for the esterification of tertiary and primary alcohols, respectively. The esters listed in Table I are prepared analogously.

A. *t*-Butyl 3-Methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate.—A solution of 0.10 mol of the acid chloride (using proportions given above) in 1.0 l. of CH₂Cl₂ was added dropwise over a 3-hr period to a stirred solution of 92.5 g (1.25 mol) of *t*-butyl alcohol (freshly distilled from KMnO₄ and dried over molecular sieves) and 19.3 g (0.175 mol) of triethylamine (freshly distilled from phenyl isocyanate and dried over KOH pellets) in 650 ml of CH₂Cl₂ maintained under anhydrous conditions at ice bath temperature. The CH₂Cl₂ solution was washed with about 500 ml of H₂O and 100 ml of 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% NaHCO₃ and H₂O, and then treated with 20 g of activated charcoal. The suspension was filtered and evaporated to dryness. The *t*-butyl ester crystallized from ether to give a total yield of 37.5 g (75%) of needles, mp 78-80°. From the neutral and basic washes was recovered 7.0 g of a mixture of Δ² and Δ³ acids.

The nmr spectrum of the Δ² ester [δ (CDCl₃) C-2 H at 5.92, C-4 H at 4.66, -OC(CH₃)₃ at 1.50 ppm] was consistent with the proposed structure.

B. *p*-Methoxybenzyl 3-Methyl-7-(phenoxyacetamide)-2-cephem-4-carboxylate.—A solution of 2 mmol of the acid chloride

in 20 ml of alcohol-free CHCl₃ was added dropwise over a 1-hr period to a stirred solution of 0.300 g (2.2 mmol) of *p*-methoxybenzyl alcohol and 0.300 g of triethylamine maintained at -50 to -75°. The solution was washed with H₂O and then 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% NaHCO₃, dried over Na₂SO₄, and evaporated to dryness. The residue was crystallized from CCl₄ as needles, mp 108-110°. The nmr spectrum (C-2 H at 5.90, C-4 H at 4.80 ppm) was identical with that of authentic material.²

Chemistry of Cephalosporin Antibiotics.

XIX. Transformation of Δ²-Cephem to Δ³-Cephem by Oxidation-Reduction at Sulfur

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A recent report from our laboratory details the final steps by which a penicillin can be converted into a cephalosporin.¹ A vital sequence in this synthesis is the conversion of a Δ²-cephem ester (1) to a Δ³-cephem ester (3) *via* the sulfoxide 2. This process utilizes the concept that β,γ-unsaturated sulfoxides are thermodynamically more stable than the corresponding α,β-unsaturated sulfoxides.²

By contrast, an equilibrium mixture of cephem isomers before oxidation contains largely the unnatural

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