when 50, 70, and 90% of the water had been added. The results are shown in the Table I.

TABLE I

Water, added, %	Diketone, labeled with one ^{18}O, %	Ketone, % ^{18}O
0	19.24	30.2
30	13.70	29.4
50	11.25	28.9
70	7.31	27.4
90	5.84	26.3

Acknowledgment.—The author is indebted to the Netherlands Organization for the Advancement of Pure Research (Z.W.O) for the sponsoring of this work. A NATO grant for the purchase of ^{18}O is gratefully acknowledged. It is with pleasure that the author expresses his gratitude to Dr. N. C. Rol (Shell Research N.V., Amsterdam) and Dr. Klebe, Dr. Van Thuyl, and Mr. Van Houte in this laboratory, who spent a great deal of time on the measurement of ^{18}O labels, to Professor W. Parker (Stirling) and to Professor H. Wynberg (Groningen) for their help in improving the presentation of this paper, and to Professor E. Heilbronner (Basel) whose gift of labeled water enabled us to do some experiments with highly labeled selenium dioxide. This work was done in the department of Professor L. J. Oosterhoff.

Registry No.—1, 4695-62-9; 2, 40514-83-8; 3, 21252-46-0; 4, 7378-37-2; 5, 40550-41-2; 6, 40550-42-3; 7, 40550-43-4; 8, 40550-44-5; water-^{18}O, 14314-42-2; selenium dioxide, 7446-08-4.

Chemistry of Cephalosporin Antibiotics. XXVII. 3-Methylenecephams

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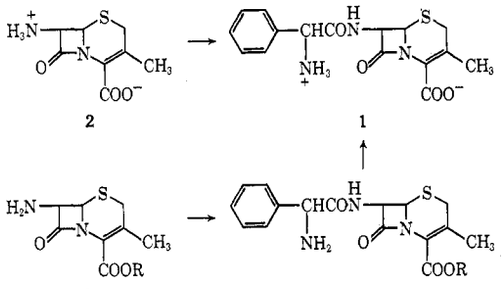
Cephalosporanic acids, in which the acetoxy group is displaced by sulfur nucleophiles, were reduced to 3-methylenecephams. Esterification procedures are described for preparing both 3-methylenecepham and 3-methyl-3-cephem esters. 7-Amino-3-methylenecepham-4-carboxylic acid and its esters were isomerized to 7-ADCA and 7-ADCA esters, respectively.

We have had considerable interest in recent years in developing new synthetic routes to deacetoxycephalosporins. A principal member of this series of antibiotics is cephalexin[1] (**1**). Syntheses of this orally active compound include acylations of either 7-aminodeacetoxycephalosporanic acid (7-ADCA, **2**)[2] obtained by hydrogenolysis of 7-ACA[3] or 7-aminodeacetoxycephalosporanic acid esters (**3**)[4] produced in the ring expansion of penicillin sulfoxides.[5] This paper reports the preparation of 3-methylenecephams[6] and their conversions to **2** and **3**.



2 **1** **3**

We anticipated that a selective desulfurization of cephalosporins in which the acetoxy group at C_3 methylene has been displaced by sulfur nucleophiles (**4**) would lead to deacetoxycephalosporins (**5**). While some 3-methyl-3-cephems (**5**) indeed formed in the treatment of these sulfur-derivatized cephalosporins with Raney nickel, 3-methylenecephams (**6**) constituted the major products. Other reducing conditions, notably zinc–formic acid–DMF, were also effective in this conversion.

The nmr spectra of 3-methylenecephams show a singlet at τ 4.9 for the C_4 proton and a doublet near τ 4.7 for the *exo*-methylene grouping. The uv chromophore at 268 mμ, characteristic of β-lactam-Δ^3-unsaturation system in cephalosporins, is not seen with 3-methylenecephams. 3-Methylenecepham acids are devoid of antibiotic activity.

Earlier reports of 3-methylenecephams include an isolation of methyl 7-phenoxyacetamido-3-methylenecepham-4-carboxylate as a minor product with 7-phenoxyacetamidodeacetoxycephalosporin methyl ester from ring expansion of penicillin V sulfoxide methyl ester.[6a] More recently Ochiai, *et al.*, published a reductive cleavage of the acetoxy group in cephalosporanic acids using chromium(II) salts that led to 3-methylenecephams in quite respectable yield.[6f]

The starting materials (**4**) were prepared by known procedures.[7] A variety of cephalosporanic acids were treated with selected nucleophiles (such as thiourea, thiobenzoic acid, potassium ethyl xanthate, and sodium thiosulfate) in neutral, aqueous solutions at 50° for 20 hr. Two separate reductive cleavages of the CH_2–S bond at C-3 in **4** were conducted.

(1) Cephalexin is the generic name for 7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid; cephalexin monohydrate, Keflex, Lilly.

(2) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, **12**, 310 (1969).

(3) R. J. Stedman, K. Severed, and J. R. E. Hoover, *J. Med. Chem.*, **7**, 117 (1964).

(4) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971).

(5) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); **91**, 1401 (1969).

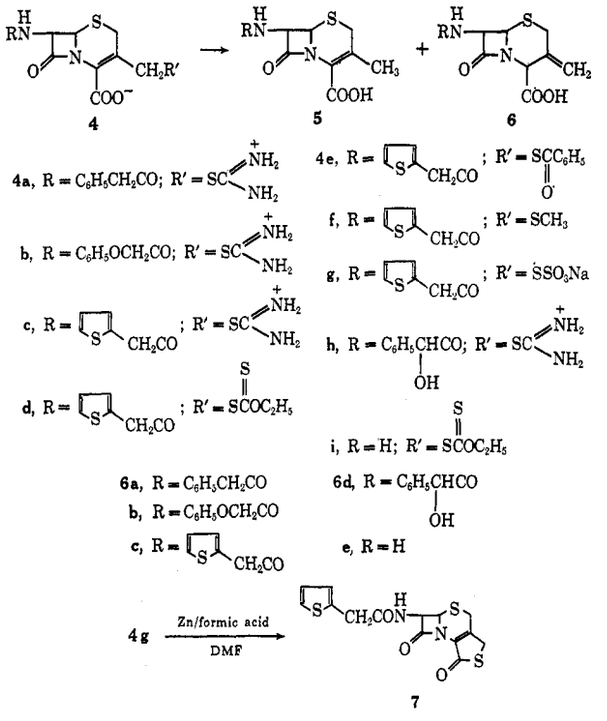
(6) (a) R. B. Morin, private communication, 1962; U. S. Patent 3,275,626 (1966); (b) M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asaki, *Tetrahedron Lett.*, 2341 (1972); (c) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and T. Kaneko, *ibid.*, 2345 (1972); (d) M. Ochiai, O. Aki, A. Morimoto, and T. Okada, *ibid.*, 3241 (1972); (e) M. Ochiai, E. Mizuto, O. Aki, A. Morimoto, and T. Okada, *ibid.*, 3245 (1972); (f) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and H. Shimadzu, *J. Chem. Soc., Chem. Commun.*, 800 (1972).

(7) (a) J. D. Cocker, B. 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.*, 5015 (1965); (b) E. M. Van Heyningen and C. N. Brown, *J. Med. Chem.*, **8**, 174 (1965); (c) Netherlands Patent 6,916,634 (1970).

In method A, commercial Raney nickel was used in aqueous ethanol solutions with **4**, under low pressure, room temperature, and overnight hydrogenation conditions.

In method B, zinc dust in tetrahydrofuran–formic acid solutions of **4**, containing catalytic dimethylformamide, were stirred at room temperature overnight. Mixtures of solvents (sometimes including water) were chosen that effectively solubilized the starting material.

The Raney nickel reduction generally gave high yields of 3-methyl-3-cephems (**5**) and 3-methylenecephams (**6**) in a product ratio of 1:4–1:5[8] from iso-

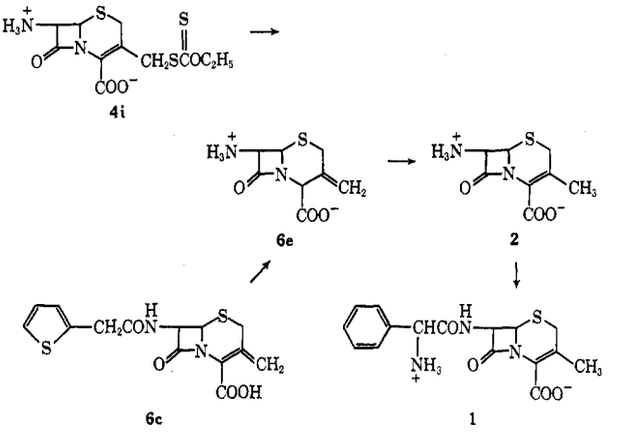


thiouronium (**4a,b,c,h**), xanthate (**4d,i**), and Bunte (**4g**) derivatives but were incomplete (generally about 50–60% conversions) with thiobenzoate (**4e**) and sulfide (**4f**) derivatives.

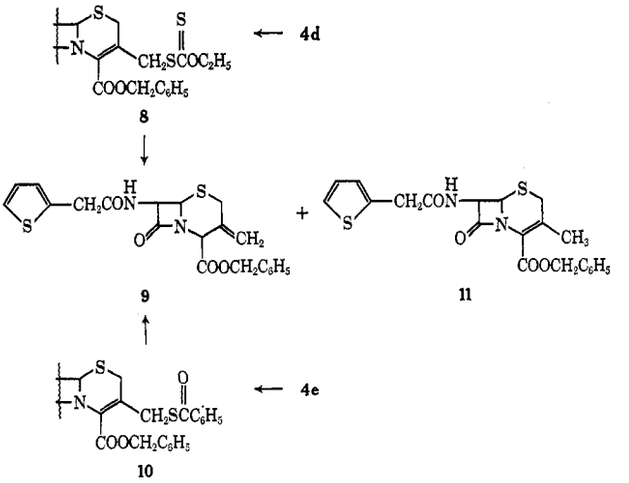
The zinc–formic acid–DMF reduction effectively reduced all starting materials except the Bunte salt (**4g**). The acidic conditions of this reaction converted **4g** largely to thiolactone **7**. Also, the zinc–formic acid–DMF reduction often yielded a nearly 1:1 product distribution[8] of **5** and **6** from thiobenzoates such as compound **4e**.

It should be noted that in contrast to the method of Ochiai, *et al.*,[6] which converts cephalosporanic acids to 3-methylene cephams, neither Raney nickel nor zinc–formic acid–DMF produced more than minor amounts of 3-methylenecephams and deacetoxycephalosporanic acids from cephalosporanic acids.

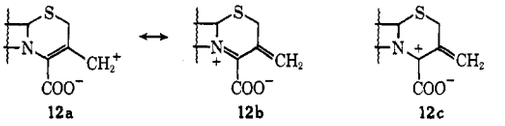
The 3-methylenecepham nucleus (**6e**) was obtained by two different routes. Compound **4i**, prepared by a modification of a reported procedure,[9] was subjected to the Raney nickel reduction conditions. Product **6e** was precipitated from concentrated water solutions at its isoelectric point. Alternatively, the side chain of 3-methylenecepham **6c** was removed in the imino chloride reaction,[10] with silylation[11] and with mixed anhydride[12] protection of the C_4-carboxyl group, to afford **6e**.



An interesting variant of the reduction of these sulfur-derivatized cephalosporins is the reduction of their C_4-esterified analogs. When treated with Raney nickel, the benzyl ester of the xanthate derivative **8** gave a product mixture that was 80% **9** and 20% **11** as determined from the nmr spectrum. Similarly, zinc–formic acid–DMF converted the benzyl ester of the thiobenzoate derivative **10** to a mixture of **9** and **11** in a 2:3 product ratio, as detected in the nmr spectrum.



A carbonium ion (**12a**) stabilized by resonance forms **12b** and **12c** has been suggested as a probable inter-



mediate in the nucleophilic displacement of the acetoxy group of cephalosporanic acids in their free acid form and in aqueous solutions.[7a] The same carbonium ion was invoked as an initial step in the formation of 3-methylenecephams by chromium(II) reductions of

(8) Product ratio was assessed by silica gel tlc (Me_2CO–HOAc, 16:1, and MeCN–H_2O, 7:3) and by nmr analysis of crude reaction products.

(9) U. S. Patent 3,446,803 (1969).

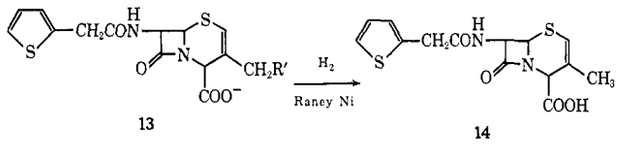
(10) F. M. Huber, R. R. Chauvette, and B. G. Jackson in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, Chapter 2.

(11) B. Fechtig, H. Peter, H. Bickel, and E. Vischer, *Helv. Chim. Acta*, **51**, 1108 (1968).

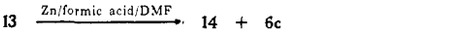
(12) R. R. Chauvette, H. B. Hayes, G. L. Huff, and P. A. Pennington, *J. Antibiot. (Tokyo)*, **XXV**, 248 (1972).

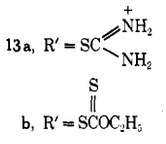
cephalosporins, as free acids and in aqueous media.[6f] Our results with **8** and **10** indicate that, if such a carbonium ion intermediate were involved at all, it does not require the presence of a free carboxyl group at C_4 during C–S bond cleavage at the C_3 CH_2.

As an extension of these reduction studies, we prepared isothiouronium salt **13a** and xanthate **13b** derivatives in the 2-cephem series. The reduction of **13a** and **13b** with Raney nickel gave exclusively the 3-methyl-2-cephem compounds **14**. Zinc–formic acid–DMF reduction of these led to mixtures of **14** and the



13 **14**

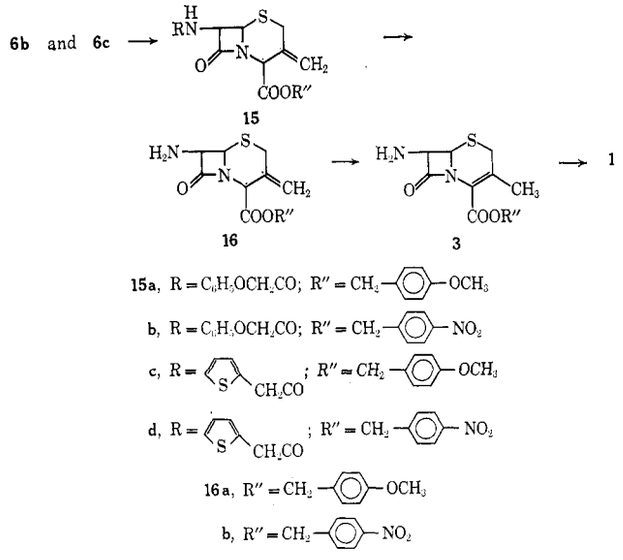




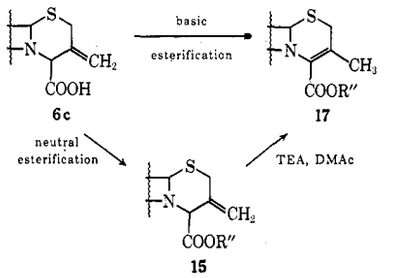
3-methylenecepham **6c** in 6:4–7:3 product ratios as calculated from their nmr spectra.

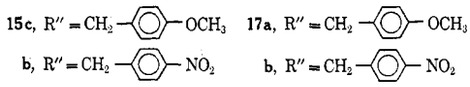
Both **6b** and **6c**, as *p*-methoxybenzyl (**15a** and **15c**) and *p*-nitrobenzyl (**15b** and **15d**) esters, smoothly underwent side-chain cleavage reactions to their corresponding 7-amino-3-methylenecepham esters **16a** and **16b**.

Esters **15a–d** were prepared using exactly 1 equiv of base in coupling reactions of 3-methylenecepham acids



with benzyl bromides. The same esterification, in the presence of excess base, resulted in double-bond isomerization, giving rise to deacetoxycephalosporin esters **17**. Predictably, 3-methylenecepham esters **15**, dissolved in dimethylacetamide containing a few drops of triethylamine and stored at room temperature overnight, converted to deacetoxycephalosporin esters **17**. Thus, **6c** afforded the *p*-methoxybenzyl ester **17a** and *p*-nitrobenzyl ester **17b** of deacetoxycephalothin either directly or *via* the 3-methylenecepham esters **15** followed by an isomerization step.





This conversion of 3-methylenecephams to 3-methyl-3-cephems effectively provided a new, efficient alternate synthesis of cephalexin. Trimethylsilylation of the 3-methylenecepham nucleus (**6e**), under basic conditions, led to the isolation of **2** in nearly quantitative yield. Its *p*-nitrobenzyl ester (**16b**), as a hydrochloride, was isomerized to **3** in high yield in dimethylacetamide containing triethylamine in excess of 1 equiv.

Alternately, hexamethyldisilazane reacted with 7-(thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (**6c**) to simultaneously protect the C_4 carboxyl group and isomerize the double bond by reason of its basicity. The reaction mixture was subjected to the imino chloride side-chain cleavage reaction, leading to the isolation of 7-ADCA (**2**) in 75% overall yield.

Nmr, ir, and uv spectra of both 7-ADCA (**2**) and 7-ADCA ester (**3**) obtained from the reactions just described were identical with those of authentic material. Since both these compounds (**2** and **3**) were integral parts of earlier syntheses,[2,4] this work represents another synthesis of cephalexin from cephalosporanic acids *via* 3-methylenecephams.

Experimental Section[13]

Reduction of Compounds 4a–k, 8, 10, 13a, and 13b. Method A.—3-Amidinothiomethyl-7-(phenoxy-2-acetamido)-3-cephem-4-carboxylic acid inner salt (**4b**), 1 g (2.4 mmol), was dissolved in 50 ml of H_2O and 50 ml of EtOH and hydrogenated at room temperature overnight in a Parr apparatus, using 45 psi of H_2 and 6 g of Raney nickel. The catalyst was filtered and washed with alcohol. The filtrate and wash were combined and concentrated *in vacuo* to remove the alcohol. The aqueous residue was slurried with EtOAc, cooled in ice, and acidified to pH 2.5 with concentrated HCl. The EtOAc solution was separated, washed with H_2O, dried ($MgSO_4$), and concentrated to a smaller volume for crystallization. Yield of 7-(phenoxy-2-acetamido)-3-methylenecepham-4-carboxylic acid (**16b**) was 650 mg (82%).

Method B.—3-Benzoylthiomethyl-7-(thiophene-2-acetamido)-3-cephem-4-carboxylic acid sodium salt (**4e**), 5 g (10 mmol), was dissolved in a mixture of 55 ml of THF, 15 ml of H_2O, 15 ml of formic acid, and 15 ml of DMF. Zinc dust, 6.5 g (100 mmol), was added and the mixture was stirred at room temperature overnight. The spent zinc was filtered and washed with THF. The filtrate and wash were combined and concentrated *in vacuo* to remove lower boiling solvents. The aqueous residue was extracted with EtOAc. The EtOAc solution was washed with HCl to remove DMF and with H_2O and then dried ($MgSO_4$). The EtOAc solution was either concentrated *in vacuo* to about 20 ml and cooled in ice or exchanged for CH_2Cl_2 for fractional crystallization of 7-(thiophene-2-acetamido)-3-

(13) Whenever possible, a single exemplifying experimental description is given as it applies in a general way to numerous compounds. Characterization data for individual products appears in Table I. Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed in the table.

TABLE I

Compd	Solvent of crystallization and mp, °C	Characterization data
6a	EtOAc 158–159	Nmr (100 Mc, DMSO-d_6) τ 6.65-6.32 (AB q, s, 4 H, C-2 H_2 and α-CH_2), 4.88 (s, 1 H, C-4 H), 4.80–4.70 (s, d, 3 H, C-3 CH_2 and C-6 H), 4.55 (q, 1 H, C-7 H), 2.73 (s, 5 H, aromatic H), and 0.92 (d, 1 H, C-7 NH).
6b	EtOAc 182–183	Nmr (A60 Mc, DMSO-d_6) τ 6.49 (s, 2 H, C-2 H_2), 5.40 (s, 2 H, α-CH_2), 4.90 (s, 1 H, C-4 H), 4.80–4.40 (m, 4 H, C-3 CH_2, C-6 H, and C-7 H), 3.20–2.60 (m, 5 H, aromatic H), and 0.92 (d, 1 H, C-7 NH).
6c	CH_2Cl_2 178	Nmr (A60 Mc, DMSO-d_6) τ 6.49 (AB q, 2 H, C-2 H_2), 6.24 (s, 2 H), α-CH_2), 4.90 (s, 1 H, C-4 H), 4.80–4.41 (m, 4 H, C-6 H, C-3 CH_2, and C-7 H), 3.12–2.55 (m, 3 H, aromatic H), and 0.98 (d, 1 H, C-7 NH).
6d	EtOAc	Nmr (A60 Mc, D_2O, $NaHCO_3$) τ 6.60 (AB q, 2 H, C-2 H_2), 5.02 (s, 1 H, C-4 H), 4.8-4.5 (m, 5 H, C-3 CH_2, α-CH, C-6 H, and C-7 H), 2.55 (s, 5 H, aromatic H).
6e	H_2O >144° dec	Nmr (A60 Mc, DMSO-d_6) τ 6.52 (AB q, 2 H, C-2 H_2), 5.50 (d, 1 H, C-6 H), 5.11 (s, 1 H, C-4 H), 4.9–4.8 (m, 3 H, C-3 CH_2 and C-7 H), and 4.2 (broad s, washed out by D_2O).
7	EtOAc	Nmr (100 Mc, DMSO-d_6) τ 6.20 (s, 2 H, C-2 H_2), 6.13 (s, 2 H, α-CH_2), 5.67 (s, 2 H, C-3 CH_2), 5.89 (d, 1 H, C-6 H), 4.20 (q, 1 H, C-7 H), 3.1–2.55 (m, 3 H, aromatic H), and 0.83 (d, 1 H, C-7 NH).
15a	$MeCl_2$–Et_2O 108–109	Nmr (T60 Mc, $CDCl_3$) τ 6.66 (AB q, 2 H, C-2 H_2), 6.21 (s, 3 H, p-OCH_3), 5.50 (s, 2 H, α-CH_2), 4.92–4.50 (m, 6 H, C-4 H, C-3 CH_2, ester CH_2, and C-6 H), 4.35 (q, 1 H, C-7 H), and 3.15–2.55 (m, 10 H, aromatic H and C-7 NH).
15b	EtOAc–Et_2O 84–94 dec	Nmr (A60 Mc, $CDCl_3$) τ 6.58 (AB q, 2 H, C-2 H_2), 5.47 (s, 2 H, α-CH_2), 4.80–4.50 (m, 6 H, C-4 H, C-3 CH_2, ester CH_2, and C-6 H), 4.25 (q, 1 H, C-7 H), 3.20–1.65 (m, 10 H, aromatic H and C-7 NH).
15c	EtOAc 114	Nmr (A60 Mc, $CDCl_3$) τ 6.65 (q, 2 H, C-2 H_2), 4.20 (s, 5 H, p-OCH_3 and α-CH_2), 4.95–4.75 (m, 5 H, C-4 H, C-3 CH_2, and ester CH_2), 4.66 (d, 1 H, C-6 H) 4.38 (q, 1 H, C-7 H), and 3.3–2.6 (m, 8 H, aromatic H and C-7 NH).
15d	EtOAc 139–141	Nmr (A60 Mc, DMSO-d_6) τ 6.42 (s, 2 H, C-2 H_2), 6.18 (s, 2 H, α-CH_2), 4.7–4.3 (m, 7 H, C-4 H, ester CH_2, C-3 CH_2, C-6 H, and C-7 H), 3.1–1.6 (m, 7 H, aromatic H), and 0.82 (d, 1 H, C-7 NH).
16a (tosylate)	EtOAc EtOH–Et_2O	Nmr (A60 Mc, DMSO-d_6) τ 7.69 (s, 3 H, p-CH_3), 6.41 (2 d, 2 H, C-2 H_2), 6.23 (s, 3 H, p-OCH_3), 5.0 (d, 1 H, C-6 H), 4.85–4.55 (m, 6, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 3.2–2.2 (2 q, 8 H, aromatic H).
16a (HCl)	Me_2Cl_2 EtOH–Et_2O >165 dec	Nmr (T60 Mc, DMSO-d_6) τ 6.47 (s, 2 H, C-2 H_2), 6.23 (s, 3 H, p-OCH_3), 5.12 (d, 1 H, C-6 H), 4.9–4.6 (m, 6 H, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 2.86 (q, 4 H, aromatic H).
16b (tosylate)	EtOAc EtOH–Et_2O 145–182 —dec	Nmr (T60 Mc, DMSO-d_6) τ 7.70 (s, 3 H, p-CH_3), 6.39 (s, 2 H, C-2 H_2), 4.98 (d, 1 H, C-6 H), 4.7–4.3 (m, 6 H, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 2.95–1.68 (2 q, 8 H, aromatic H).
16b (HCl)	$MeCl_2$ EtOH–Et_2O 160–176 dec	Nmr (A60 Mc, DMSO-d_6) τ 6.34 (AB q, 2 H, C-2 H_2), 4.98 (d, 1 H, C-6 H), 4.7–4.4 (m, 6 H, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 2.0 (q, 4 H, aromatic H).
17a	EtOAc 160	Nmr (A60 Mc, $CDCl_3$) τ 7.92 (s, 3 H, C-3 CH_3), 6.75 (AB q, 2 H, C-2 H_2), 6.21 (s, 3 H, p-OCH_3), 6.18 (s, 2 H, α-CH_2), 5.11 (d, 1 H, C-6 H), 4.83 (s, 2 H, ester CH_2), 4.29 (q, 1 H, C-7 H), and 3.21–2.60 (m, 8 H, aromatic H and C-7 NH).
17b	EtOAc 217	Nmr (A60 Mc, DMSO-d_6) τ 7.91 (s, 3 H, C-3 CH_3), 6.47 (AB q, 2 H, C-2 H_2), 6.20 (s, 2 H, α-CH_2), 4.89 (d, 1 H, C-6 H), 4.60 (s, 2 H, ester CH_2), 4.30 (q, 1 H, C-7 H), 3.1–1.65 (m, 7 H, aromatic H), and 0.88 (d, 1 H, C-7 NH).

methylenecepham-4-carboxylic acid (6c) (Table I), 1.2–2.0 g (35–42%).

7-Amino-3-ethoxythionocarbonylthiomethyl-3-cephem-4-carboxylic Acid Sodium Salt (4i).—In a modification of the literature preparation,[9] 80% pure 7-ACA, 6.9 g (20 mmol), was dissolved in 69 ml of H_2O containing sodium bicarbonate, 2.1 g (25 mmol). Ethylxanthic acid potassium salt, 4.0 g (25 mmol), was added and the mixture was heated in an oil bath at 65° for 4 hr. The product crystallized from the cooled reaction mixture, 2.5 g. A second, equal size crop of product was obtained on adjusting the pH to 5.

7-Amino-3-methylenecepham-4-carboxylic Acid (6e). Method A.—7-Amino-3-ethoxythionocarbonylthiomethyl-3-cephem-4-carboxylic acid (4i), 11 g (31 mmol), was dissolved in 260 ml of $NaHCO_3$ solution and 40 ml of EtOH and hydrogenated in the usual way with 66 g of Raney nickel. The catalyst was filtered and washed with H_2O. The combined filtrate and wash were cooled to ice temperature and adjusted to pH 3.5 with concentrated HCl. A 2.2-g precipitate of unreacted starting material was separated. Concentration to near dryness *in vacuo* precipitated the crude product. Recrystallization from H_2O afforded 4.5 g (67%) of 6e.

TABLE II

Compd	Solvent of crystallization and mp, °C	Analysis
6a	EtOAc 158–159	*Anal.* Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.84; H, 5.04; N, 8.31.
6b	EtOAc 182–183	*Anal.* Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.38; H, 4.86; N, 8.09.
6c	CH_2Cl_2 178	*Anal.* Calcd for $C_{14}H_{14}N_2O_4S_2$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.58; H, 4.36; N, 8.25.
4h	H_2O 189–200 dec	*Anal.* Calcd for $C_{17}H_{18}N_4O_5S_2 \cdot H_2O$: C, 46.35; H, 4.57; N, 12.72. Found: C, 46.54; H, 4.82; N, 12.67.
6d	EtOAc	*Anal.* Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04. Found: C, 55.29; H, 4.91; N, 7.75.
6e	H_2O >144 dec	*Anal.* Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 45.12; H, 4.73; N, 13.11.
7	EtOAc	*Anal.* Calcd for $C_{14}H_{12}N_2O_3S_3$: C, 47.71; H, 3.43; N, 7.94; S, 27.29. Found: C, 47.77; H, 3.60; N, 7.67; S, 27.05.
8	EtOAc–Et_2O 150–152	*Anal.* Calcd for $C_{24}H_{24}N_2O_5S_4 \cdot {}^1/_2Et_2O$: C, 53.30; H, 4.99; N, 4.78. Found: C, 53.80; H, 4.81; N, 4.99.
10	EtOAc 150–151	*Anal.* Calcd for $C_{28}H_{24}N_2O_5S_3$: C, 59.56; H, 4.28; N, 4.96. Found: C, 59.53; H, 4.57; N, 5.12.
13a	H_2O ~194 dec	*Anal.* Calcd for $C_{15}H_{16}N_4O_4S_3$: C, 43.68; H, 3.91; N, 13.58. Found: C, 43.48; H, 3.94; N, 13.32.
13b	H_2O ~154 dec	*Anal.* Calcd for $C_{17}H_{17}N_2O_5S_4Na \cdot H_2O$: C, 40.94; H, 3.84; N, 5.61. Found: C, 41.30; H, 4.30; N, 5.76.
15a	$MeCl_2$–Et_2O 108–109	*Anal.* Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.53; H, 5.16; N, 5.98. Found: C, 61.29; H, 4.94; N, 5.70.
15b	EtOAc–Et_2O 84–94 dec	*Anal.* Calcd for $C_{23}H_{21}N_3O_7S$: C, 57.14; H, 4.38; N, 8.69. Found: C, 56.86; H, 4.32; N, 8.44.
15c	EtOAc 114°	*Anal.* Calcd for $C_{22}H_{22}N_2O_5S_2$: C, 57.64; H, 4.84; N, 6.11. Found: C, 57.76; H, 4.94; N, 6.02.
15d	EtOAc 139–141	*Anal.* Calcd for $C_{21}H_{19}N_3O_6S_2$: C, 53.27; H, 4.04; N, 8.87. Found: C, 52.99; H, 3.98; N, 8.93.
16a tosylate	EtOAc EtOH–Et_2O	*Anal.* Calcd for $C_{23}H_{26}N_2O_7S_2$: C, 54.53; H, 5.17; N, 5.53. Found: C, 54.33; H, 5.05; N, 5.47.
16a (HCl)	Me_2Cl_2 EtOH–Et_2O >165 dec	*Anal.* Calcd for $C_{16}H_{19}N_2O_4SCl$: C, 51.82; H, 5.16; N, 7.55. Found: C, 51.65; H, 5.04; N, 7.72.
16b tosylate	EtOAc EtOH–Et_2O 145–182 dec	*Anal.* Calcd for $C_{22}H_{23}N_3O_8S_2$: C, 50.66; H, 4.45; N, 8.06. Found: C, 50.41; H, 4.51; N, 7.86.
16b (HCl)	$MeCl_2$ EtOH–Et_2O 160–176 dec	*Anal.* Calcd for $C_{15}H_{16}N_3O_5SCl$: C, 46.69; H, 4.18; N, 10.89. Found: C, 46.40; H, 4.20; N, 10.62.
17a	EtOAc 160°	*Anal.* Calcd for $C_{22}H_{22}N_2O_5S_2$: C, 57.64; H, 4.84; N, 6.11. Found: C, 57.39; H, 5.11; N, 5.89.
17b	EtOAc 217°	*Anal.* Calcd for $C_{21}H_{19}N_3O_6S_2$: C, 53.28; H, 4.05; N, 8.88. Found: C, 53.01; H, 4.22; N, 8.94.

Method B.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c), 1.7 g (5 mmol), was suspended in 40 ml of $MeCl_2$ and treated with diethylaniline, 850 mg (5.7 mmol), acetyl chloride, 430 mg (5.5 mmol), and 4 drops of DMF. The starting material went into solution within 5 min. The mixture was cooled in a carbon tetrachloride–Dry Ice bath for addition of diethylaniline, 1.28 g (8.5 mmol), and phosphorus pentachloride, 1.2 g (5.8 mmol). After 1.5 hr, 12 ml of cold MeOH was added followed by 20 ml of H_2O after another 1.5-hr reaction time. The cooling bath was removed and the aqueous layer was separated, washed with EtOAc, adjusted to pH 3.6, and evaporated to near dryness *in vacuo*. The crystalline residue was triturated with acetone to remove diethylaniline, leaving 700 mg of 6e.

Esterification of 4d, 4e, 6b, and 6c with a Stoichiometric Amount of Base.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c) sodium salt, 700 mg (2 mmol), was dissolved in 7 ml of dimethylacetamide and treated with anisyl bromide, 600 mg (3 mmol), at room temperature overnight. The mixture was poured into H_2O–EtOAc. The EtOAc layer was separated, washed successively with 5% HCl, 5% $NaHCO_3$ solution, and H_2O, dried ($MgSO_4$), concentrated to a small volume *in vacuo*, and cooled for crystallization. The yield of *p*-methoxybenzyl 7-(thiophene-2-acetamido)-3-methylenecepham-4-carboxylate (15c) was 570 mg (62%).

Esterification of 6c with Excess Base.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c), 3.4 (10 mmol), was dissolved in 34 ml of DMAc. *p*-Nitrobenzyl bromide, 2.4 g (11 mmol), and triethylamine, 2.2 g (22 mmol), were added and the mixture was stored at room temperature overnight. The precipitated triethylamine hydrobromide was filtered. The filtrate was added to cold H_2O–EtOAc. The EtOAc layer was separated, washed successively with cold 5% HCl, 5% $NaHCO_3$ solution, and water, and dried ($MgSO_4$). The EtOAc solution was concentrated *in vacuo* to a smaller volume for crystallization. Yield of *p*-nitrobenzyl 7-(thiophene-2-acetamido)-3-methyl-3-cephem-4-carboxylate (17b) was 3.0 g (64%).

Side Chain Cleavage of 3-Methylenecepham Esters 15a–d.—*p*-Nitrobenzyl 7-(thiophene-2-acetamido)-3-methylenecepham-4-carboxylate (15d), 12 g (25 mmol), was dissolved in 130 ml of CH_2Cl_2. Dry pyridine, 2.45 g (31 mmol), and phosphorus pentachloride, 6.0 g (25 mmol), were added. The mixture was stirred at room temperature for 2 hr. After the reaction mixture was cooled in an ice–H_2O bath, 12.5 ml of isobutyl alcohol was added. The mixture was stirred in the cold for 2 hr. The product crystallized from the reaction mixture. Filtering and washing the precipitate with CH_2Cl_2 afforded 8.6 g (90%) of *p*-nitrobenzyl 7-amino-3-methylenecepham-4-carboxylate (16b) as a hydrochloride. Alternatively, in the place of cooling the reaction mixture, cold methanol was added and then H_2O. Work-up then consisted in separating the aqueous layer and adjusting the pH to 7 in the presence of EtOAc. The EtOAc layer was separated, washed with H_2O, dried ($MgSO_4$), and treated with slightly more than 1 equiv of *p*-toluenesulfuric acid monohydrate. The product (16b) crystallized in 60% yield as a tosylate salt.

Isomerization of 3-Methylenecephams. 7-Amino-3-methyl-4-carboxylic Acid (2). Method A.—7-Amino-3-methylenecepham-4-carboxylic acid (6e), 215 mg (1 mmol), was suspended in 5 ml of MeCN and treated with an excess of *N*-trimethylsilylacetamide. Three drops of triethylamine was added to the clear solution after 45 min; 1 ml of MeOH was added after 2 hr. Addition of 0.1 *N* HCl to pH 3.6 precipitated 200 mg of product.

Method B.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c), 2 g (5.9 mmol), was dissolved in 40 ml of MeCN. Hexamethyldisilazane (6 mmol) was added and the solution was stored at room temperature for 4 days. The solvent was exchanged for $MeCl_2$, cooled to −20°, and treated with diethylaniline, 1.46 g (10 mmol), and phosphorus pentachloride,

1.3 g (6.4 mmol). The mixture was stirred for 30 min; 7 ml of MeOH was added, followed after 45 min with 17 ml of H_2O. The aqueous phase was separated, washed with $MeCl_2$, and adjusted to pH 3.6 with saturated $(NH_4)HCO_3$ solution. The precipitated 7-ADCA (2) weighed 900 mg (75% overall yield).

p-**Nitrobenzyl 7-Amino-3-methyl-3-cephem-4-carboxylate (3) Hydrochloride Salt.**—*p*-Nitrobenzyl 7-amino-3-methylenecepham-4-carboxylate (**16b**) hydrochloride salt, 386 mg (1 mmol), was dissolved in 5 ml of DMAc containing triethylamine, 198 mg (2 mmol). The mixture was stored at room temperature for 3 hr. The reaction mixture was poured into H_2O–EtOAc. The EtOAc layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to a volume of about 10 ml; 10 ml of 0.1 *N* HCl in EtOAc was added. A crystalline precipitate formed immediately. The product was filtered, washed with EtOAc, and vacuum dried, yield 320 mg (83%).

See Table II for analytical data.

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Polynitroalkyl Ethers[1]

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Polynitroethyl ethers were prepared by nitration of the corresponding oximes. Thus, nitration of (2-fluoro-2,2-dinitroethoxy)acetaldoxime followed by oxidation of the nitroso intermediate yielded 2-fluoro-2,2-dinitroethyl 2,2-dinitroethyl ether (1). Fluorination and chlorination of 1 yielded bis(2-fluoro-2,2-dinitroethyl) and 2-chloro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethyl ether, respectively. Formaldehyde and 1 yielded 3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropyl formal. 2-Fluoro-2,2-dinitroethyl glycidyl ether reacted with 2-fluoro-2,2-dinitroethanol to give 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol, which was oxidized with chromic acid to 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone. Nitration of the oxime of this ketone and oxidation of the nitroso intermediate yielded 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropane. Decomposition of 2-fluoro-2,2-dinitroethanol in alkaline solutions is suppressed by formaldehyde. Under these conditions propargyl bromide gave 2-fluoro-2,2-dinitroethyl propargyl ether. Five 1-(2-fluoro-2,2-dinitroethoxy)-2-propanol derivatives, $FC(NO_2)_2CH_2OCH_2CH(OH)CH_2X$ [X = Cl, Br, I, ONO_2, $OCOC(CH_3)_3$], were synthesized by treating 2-fluoro-2,2-dinitroethyl glycidyl ether with HX. Three of these were oxidized to the corresponding acetone derivatives, $FC(NO_2)_2CH_2OCH_2COCH_2X$ [X = Cl, ONO_2, $OCOC(CH_3)_3$].

Although 2-fluoro-2,2-dinitroethanol can be alkylated in aqueous alkaline solution by reagents such as allyl bromide, methyl sulfate, and simple epoxides to give the corresponding 2-fluoro-2,2-dinitroethyl ethers,[2] alkylating agents with nitro substituents do not yield polynitroalkyl ethers.[3] 2-2-Dinitro alcohols cannot be dehydrated to the corresponding ethers,[4] and bis(2,2-dinitroalkyl) ethers, therefore, must be synthesized indirectly. A recent patent[5] describes the synthesis of bis(2-fluoro-2,2-dinitroethyl) ether in low yield starting with bis(2-iodoethyl) ether. The ether was treated with silver nitrite to give bis(2-nitroethyl) ether. The oxidative nitration of bis(2-nitroethyl) ether with formaldehyde present gave a mixture of methylol derivatives of trinitro- and tetranitrodiethyl ether which was fluorinated to give bis(2-fluoro-2,2-dinitroethyl) ether.

2-Fluoro-2,2-dinitroethyl 2,2-dinitropropyl ether[2] was prepared by nitration of (2-fluoro-2,2-dinitroethoxy)-acetone oxime followed by oxidation of the resulting nitroso intermediate with hydrogen peroxide. The precursor ketone was obtained by oxidation of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether. In the present paper the generality of this route to 2,2-dinitroalkyl ethers is explored.

Although aryldinitromethanes can be readily obtained from aromatic aldoximes[6] by nitration and oxidation, this reaction is not applicable to simple aliphatic aldoximes. It was of interest to determine whether electronegative substituents would facilitate this reaction.

(2,2-Dinitroalkoxy)acetaldehydes have not been described in the literature. A convenient starting material for their synthesis was 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol.[7] (2-Fluoro-2,2-dinitroethoxy)acetaldehyde was obtained by cleaving this diol with either periodic acid or lead tetraacetate. This aldehyde

$$FC(NO_2)_2CH_2OCH_2CH(OH)CH_2OH \xrightarrow[\text{or } Pb(OAc)_4/C_6H_6]{H_5IO_6/H_2O} FC(NO_2)_2CH_2OCH_2CHO + HCHO$$

reacted with hydroxylamine to give (2-fluoro-2,2-dinitroethoxy)acetaldoxime in 90–95% yields. The oxime was nitrated with 90% nitric acid in methylene chloride to give the deep blue nitro–nitroso derivative, which was not isolated. Oxidation of this intermediate

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