(s, thienyl CH_2) 2.1 (s, $CH_3C{=}O$); $\lambda_{max}^{H_2O}$ 235 (ϵ 10,570), 255 (ϵ 6900 sh).

Table I compares the antimicrobial activity of compound **12a** with that of 6(*R*),7(*R*)-sodium cephalothin.

Acknowledgment. We are grateful to Dr. R. W. Ratcliffe for stimulating discussions during the course of this work. We thank Dr. E. H. Thiele for the *in vitro* results reported in this paper.

References and Notes

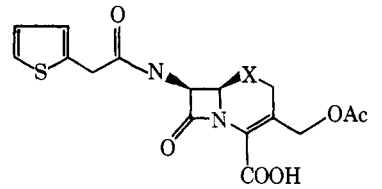
(1) Total Synthesis of β-Lactam Antibiotics. VI: R. A. Firestone, N. S. Maciejewicz, and B. G. Christensen, *J. Org. Chem.*, in press.
(2) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4645, 4649, 4653 (1973).
(3) (a) We propose the name 1-oxacephalothin for7β-thienylacetamido-1-oxadethiacephalosporanic acid. (b) A 1-oxadethiacepham has been reported. J. C. Sheehan and Miroslav Dadic, *J. Heterocycl. Chem.*, **5**, 779 (1968).
(4) R. N. Guthikonda, L. D. Cama, and B. G. Christensen, *J. Amer. Chem. Soc.*, **96**, 7584 (1974).
(5) S. Kukolja, *J. Amer. Chem. Soc.*, **93**, 6267 (1971).
(6) H. O. L. Fischer, E. Baer, and L. Feldman, *Chem. Ber.*, **63**, 1732 (1930).
(7) (a) J. C. Sheehan, D. Ben-Ishai, and J. V. Piper, *J. Amer. Chem. Soc.*, **95**, 3065 (1973); (b) S. Wolfe and M. P. Goeldner, *Tetrahedron Lett.*, 5131 (1973).

L. D. Cama, B. G. Christensen*
Merck Sharp and Dohme Research Laboratories
Division of Merck & Co., Inc.
Rahway, New Jersey 07065
Received June 29, 1974

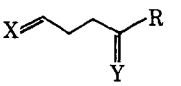
Total Synthesis of β-Lactam Antibiotics. VIII.[1a] Stereospecific Total Synthesis of (±)-1-Carbacephalothin[1b]

Sir:

As part of a program to devise convergent total syntheses of β-lactam analogs in our laboratories,[2] it was of interest to synthesize the nuclear analogs of the parent cephalosporins in which the sulfur atom is suitably substituted by simple isosteric groups. We now describe the stereospecific total synthesis of (±)-1-carbacephalothin[1b] (**1**), which embraces all the characteristic functionalities of cephalothin (**2**), except that the cephem sulfur has been replaced by methylene. Although partially substituted bicyclic analogs have been synthesized,[3] there appeared no report to date of the synthesis of the appropriately functionalized cephalosporin analog **1**. The crucial synthon **6** was synthesized as follows. 4-Pentenoyl chloride[4] reacted with diazomethane in ether (overnight, dark) to yield quantitatively 1-diazo-5-hexen-2-one (**3**): ir (μ) 4.72 (=N=N), 6.06 (C=O, C=C).[5] The diazoketone **3** decomposed in glacial acetic acid (1 hr, 60–70°) yielding the coupling product, 1-acetoxy-5-hexen-2-one (**4**) (90%): nmr 2.17 (s, CH_3), 4.67 (s, CH_2), 2.47 (m, CH_2CH_2), 4.82–6.17 (CH_2=CH); ir 5.70 (ester), 6.08 (C=C), 5.74 (C=O). Ketalization of **4** was accomplished smoothly (3 equiv of ethylene glycol, 10% *p*-TsOH by weight of ketone, benzene, 2 hr reflux) to give **5**

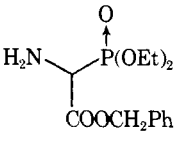


1, X = CH_2
2, X = S

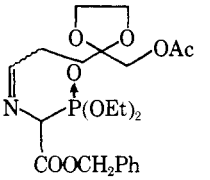


3, X = CH_2; Y = O; R = CHN_2
4, X = CH_2; Y = O; R = CH_2OAc
5, X = CH_2; Y =  ; R = CH_2OAc
6, X = O; Y =  ; R = CH_2OAc

(90%): nmr 2.03 (s, CH_3), 1.7–2.15 (m, CH_2CH_2), 3.95 (s, CH_2CH_2), 4.0 (s, CH_2), 4.8–6.1 (m, CH_2=CH); ir 5.7 (ester) 6.06 (C=C). Oxidative scission of the double bond in **5** was achieved by cautious addition of 2 equiv of sodium metaperiodate to a heterogeneous mixture of olefin **5**, and 0.06 equiv of osmium tetroxide in ether and water (24–27°, 2.5 hr). The resulting aldehyde **6** was isolated in 60% yield after chromatography:[6] nmr 2.10 (s, CH_3), 2.04–2.6 (m, CH_2CH_2), 4.0 (s, CH_2CH_2), 4.03 (s, CH_2), 9.73 (t, CHO); ir 3.66 (CH of aldehyde), 5.7 (ester), 5.79 (C=O).



7



8

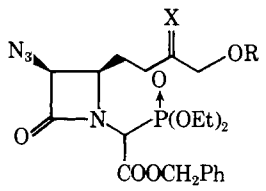
The aldehyde **6** was condensed (ether, anhydrous magnesium sulfate, 1 hr, room temperature) with the amine **7**[2a] to give the unstable Schiff base, benzyl α-(5-acetoxy-4,4-ethylenedioxypentanaldimino)diethylphosphonoacetate (**8**): nmr 1.27 (t, CH_3), 2.08 (s, CH_3), 3.96 and 4.02 (s, CH_2CH_2 and CH_2), 4.5 (d, HCP, J = 20 Hz), 5.25 (s, CH_2), 7.38 (s, Ph), 7.82 (d, d, HC=N); ir 5.72 (esters), 6.0 (C=N). While other methods failed to produce even traces of β-lactam, an addition of an ethereal solution of the freshly prepared Schiff base **8** to a mixture of 1.5 equiv each of triethylamine and azidoacetyl chloride[7] at −78° in ether and warm-up of the reaction mixture to room temperature overnight resulted in the stereospecific cycloaddition to *cis*-1-(benzyloxycarbonyldiethylphosphono)methyl-3-azido-4-(3-ethylenedioxy-4-acetoxy)butyl-2-azetidinone (**9**): 30% after chromatography; nmr (100 MHz) 2.08 (s, CH_3), 4.70 (d, N_3CH, J = 5.5 Hz), 5.0 (d, HCP, J = 24 Hz), 5.22 (s, CH_2), 7.34 (s, Ph); ir 4.70 (N_3), 5.62 (β-lactam C=O), 5.69 (esters). Notably, this stereospecificity

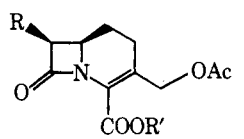
Table I. Minimum Inhibitory Concentrations (MIC) Expressed in μg/ml

Compound	*Staphylococcus aureus* 2865	*Streptococcus pyogenes* 3124	*Klebsiella sp.* 2882	*Escherichia coli* 2884	*Shigella sp.* 2880	*Salmonella schottmuelleri* 2837
15	1.56	<0.39	6.25	6.25	6.25	3.12
Na cephalothin[a] (6(*R*),7(*R*))	<0.39	<0.39	3.12	3.12	3.12	3.12

[a] Racemic Na cephalothin has approximately one-half the activity of 6(*R*),7(*R*)-sodium cephalothin.[2a]

(cis cycloaddition) is totally reversed (to transcycloaddition) if the 4-(3-ethylenedioxy-4-acetoxy)butyl side-chain in **9** is replaced by the 4-SMe group.[1a] Although attempted selective deketalization of the ketal **9** under various conditions failed, treatment with aqueous 10% sulfuric acid in glacial acetic acid (8:1, 2 hr, 50°) resulted in deketalization with concomitant selective ester hydrolysis of the acetate (not the benzyl ester or phosphonate) affording 89% of *cis*-1-(benzyloxycarbonyldiethylphosphono)methyl-3-azido-4-(3-oxo-4-hydroxy)butyl-2-azetidinone (**10**): nmr, ketal, CH_2CH_2, and acetate CH_3 disappeared; ir 2.56 (OH), 4.70 (N_3), 5.62 (β-lactam C=O), 5.72–3.80 (C=O and ester).





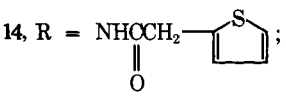
9, X =  ; R = Ac

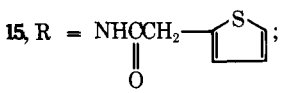
10, X = O; R = H

11, X = O; R = Ac

12, R = N_3; R′ = CH_2Ph

13, R = NH_2; R′ = H

14, R =  ; R′ = CH_3

15, R =  ; R′ = Na

Acetylation of the ketol **10** (acetyl chloride, pyridine, methylene chloride, room temperature, overnight) gave the acetoxy ketone **11** in 82.5% yield: nmr (100 MHz) 2.14 (s, CH_3), 1.25 (m; CH_3), 4.13 (m, CH_2), 4.63 (s, CH_2), 4.73 (d, N_3CH, J = 5.5 Hz), 4.99 (d, HCP, J = 24 Hz), 7.32 and 7.34 (Ph); ir 4.70 (N_3), 5.62 (β-lactam C=O), 5.70 (esters). Cyclic olefination of **11** was smoothly effected with sodium hydride in dry glyme (50°, 1.5 hr) to afford on chromatography the bicyclic (±)-benzyl 7β-azido-1-methylenedethiacephalosporanate (**12**) (62%): nmr (100 MHz), 1.98 (s, CH_3), 3.72 (m, CCHN), 4.8 and 5.07 (AB q, CH_2O), 4.85 (d, HCN_3, J = 5.5 Hz), 5.20 (s, CH_2), 7.21 (m, Ph); ir 4.7 (N_3), 5.62 (β-lactam C=O), 5.73 (esters), 6.09 (C=C). Simultaneous hydrogenolysis of the benzyl ester and reduction of azide (10% Pd-C, H_2, aqueous dioxane, 0.5 hr, room temperature, 45 psi) in **12** yielded the zwitterion, (±)-7β-amino-1-methylenedethiacephalosporanic acid (**13**): ir (Nujol), 2.94 (NH_2, OH), 5.57 (β-lactam C=O), 5.74 (acid and ester). Acylation of the amino acid **13** with 2-thienylacetyl chloride and sodium bicarbonate in aqueous acetone at 0° for 1 hr afforded (±)-7β-(2-thienyl)acetamido-1-methylenedethiacephalosporanic acid (**1**), 80% overall yield from the azido benzyl ester **12** (nmr (acetone-d_6) 2.03 (s, CH_3), 3.89 (s, CH_2), 5.50 (dd, NCHC=O, J = 5.5 Hz, J = 9 Hz), 4.8 and 5.07 (AB q, CH_2O), 8.00 (d, NH, J = 9 Hz); ir 5.7 (β-lactam C=O), 5.8 (acid and ester); *m/e* 318 (M^+ − AcOH)), which was further identified as the methyl ester (diazomethane, ethyl acetate, ether) **14** (nmr 2.05 (s, CH_3), 3.8 (s, CH_3 and CH_2), 4.8 and 5.16 (AB q, CH_2), 5.4 (dd, NCHC=O, J = 5.5 Hz, J = 9 Hz), 6.45 (d, NH, J = 9 Hz); *m/e* 392 (M^+)). The sodium salt **15** of the acid **1** was prepared by adding equimolar sodium bicarbonate to the acid **1** in water: nmr (D_2O) 2.07 (s, CH_3), 3.9 (s, CH_2C=O), 5.28 (d, NCHC=O, J = 5 Hz), 4.63 and 4.9 (AB q, CH_2); ir (Nujol) 5.67 (β-lactam C=O), 5.73 (ester), 5.98 (NHC=O), 6.22 (COO^-); uv $\lambda_{max}^{H_2O}$ 238 (ϵ 12,800), 255 (ϵ 10,440).[8] Table I compares the antimicrobial activity of compound **15** with that of 6(*R*),7(*R*)-sodium cephalothin.

Acknowledgment. We are grateful to Dr. R. W. Ratcliffe for stimulating discussion during the course of this work. We also thank Dr. E. H. Thiele for the *in vitro* results reported in this paper.

References and Notes

(1) (a) For Part VII, see L. D. Cama and B. G. Christensen, *J. Amer. Chem. Soc.*, **96**, 7582 (1974). (b) We propose this trivial name for (±)-7β-(2-thienyl)acetamido-1-methylenedethiacephalosporanic acid.
(2) (a) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4645, 4649, 4653 (1973); (b) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).
(3) (a) D. M. Brunwin, G. Lowe, and J. Parker, *Chem. Commun.*, 865 (1971); (b) D. R. Bender, L. F. Bjeldanes, D. R. Knapp, D. R. McKean, and H. Rapoport, *J. Org. Chem.*, **38**, 3439 (1973).
(4) Prepared from commercial 4-pentenoic acid and oxalyl chloride with a trace of DMF in ether, bp 126–129°, 90%; H. Wohlgemuth, *Ann. Chim. Paris*, **2** (9), 329 (1914).
(5) Unless otherwise stated, nmr solvent is $CDCl_3$, chemical shift is in δ, and AB quartets are reported as the mid-point values of the doublets and ir is neat thin film on sodium chloride disk and the bands are reported in wavelength, μ.
(6) All chromatographies were run on E. Merck silica gel columns using mixtures of benzene–ethyl acetate as eluting solvents.
(7) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).
(8) The experimental observation of the difference in uv absorptions of 261 nm (ϵ 8230) in sodium cephalothin and 255 nm (ϵ 10,440) in sodium 1-carbacephalothin (**15**) suggests that the interaction between the sulfur and enamine moiety previously postulated for cephalosporin does not occur in the case of **1**, resulting in an apparent effect on its absorption and extinction coefficient: D. M. Green, A. G. Long, P. J. May, and A. F. Turner, *J. Chem. Soc.*, 766 (1964).

R. N. Guthikonda, L. D. Cama, B. G. Christensen*
Merck Sharp and Dohme Research Laboratories
Division of Merck & Co., Inc.
Rahway, New Jersey 07065
Received June 29, 1974

Decamethoxonium, an Alkylating Analog of Decamethonium

Sir:

Decamethonium (decamethylenebis (trimethylammonium) (I)) binds tightly but reversibly to acetylcholinesterase. In the case of enzyme from the electric eel, the value of the dissociation constant of I is 3×10^{-8} M at low ionic strength.[1] Decamethoxonium (decamethylenebis(dimethyloxonium) (II)) is structurally similar to I, and the trialkyloxonium group is a highly reactive alkylating function.[2] Consequently, we expected that II might be an active-site-directed alkylating agent for acetylcholinesterase. This report describes the synthesis of II and its effect on the esterase, as well as preliminary results with another protein, acetylcholine receptor.

$(CH_3)_3\overset{+}{N}(CH_2)_{10}\overset{+}{N}(CH_3)_3$ I $(CH_3)_2\overset{+}{O}(CH_2)_{10}\overset{+}{O}(CH_3)_2$ II

1,10-Dimethoxydecane was prepared from 1,10-dibromodecane (Aldrich Chemical Co.) by refluxing the dibromo compound with a slight excess of sodium methoxide in methanol for 24 hr. After evaporation of the methanol and addition of water to the residue, the product was extracted into ether and purified by distillation at reduced pressure. II was prepared from 1,10-dimethoxydecane by alkylation with methyl iodide in the presence of silver hexafluorophosphate, after the procedure of Meerwein.[3,4] 1,10-Dimethoxydecane (3.0 ml) and, immediately afterwards, methyl iodide