Tetrahedron Letters No. 30, pp 2625 - 2628, 1974. Pergamon Press. Printed in Great Britain.

THE CHEMISTRY OF CEPHAMYCINS.[1a,1b] II.[2] NOVEL SYNTHESIS OF 3-HALOMETHYL CEPHALOSPORINS

Sandor Karady, Theresa Y. Cheng, Seemon H. Pines, and Meyer Sletzinger

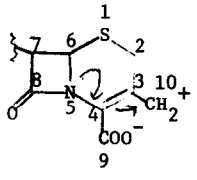
Merck Sharp & Dohme Research Laboratories, Division of

MERCK & CO., Inc., Rahway, N. J.

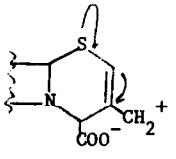
(Received in USA 25 April 1974; received in UK for publication 17 June 1974)

One of the challenges of cephalosporin chemistry is the introduction of new substituents at C_{10}[3] (C_3-methylene). Replacement of the acetoxy group of Δ^3 cephalosporin carboxylic acids by nucleophiles in an aqueous medium was reported by Cocker.[4a] The isomeric Δ^2 carboxylic acids reacted at a slower rate.[4b] However, no displacement took place with the corresponding Δ^2 and Δ^3 esters. It was postulated[4] that the reaction requires carbonium ions which are stabilized by a close negative charge in the form of ions I and II.

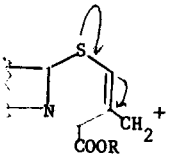
In this, and the following paper, we wish to report that the acetoxy and carbamoyloxy groups of Δ^2 cephems can be readily replaced in the presence of strong acids in a non-polar medium. The reactions proceed presumably via the sulfur stabilized carbonium ion III. The Δ^3 esters, because of the poor carbonium ion (IV) involved, do not react in this fashion.



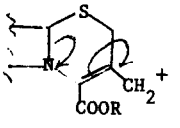
I



II



III



IV

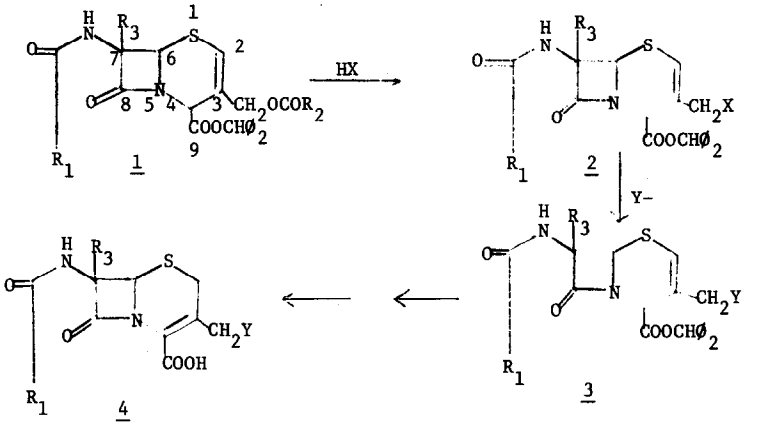
10-Bromo-2-cephem derivatives are versatile intermediates in the preparation of C_{10} substituted cephalosporins.[5,6] They are usually prepared by the radical bromination[7] of certain[8] Δ^2 desacetoxy cephalosporins.

The subject of this paper is a new simple synthesis of Δ^2-10-halo cephems. The method is based on the facile cleavage by hydrohalic acids of the allylic C_{10} oxygen bond of Δ^2 cephamycins (1a,1b) and cephalosporins (1c).

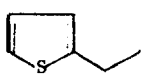
When cephamycin derivative 1a, NMR ($CDCl_3$) δ 3.20 (s, OCH_3), 4.55 (s, C_{10}-H_2), 4.90 (s, $OCONH_2$), 5.1 (d, J=2 Hz, C_4-H) 5.32 (s, C_6-H), 6.32 (d, J=2 Hz, C_2-H) or 1b was treated with a solution of HCl, HBr, or HI in methylene chloride at 0°, an ammonium halide precipitated and 10-halo compound 2a or 2b formed in good yield (60-80%). Cephalothin derivative 1c reacted similarly to afford the otherwise unavailable[8] 2c. The ease of this cleavage is illustrated by the fact that it takes place selectively in the presence of benzhydryl esters. Only with an excess of hydrohalic acid was significant ester cleavage observed.

A non-polar solvent is necessary in this transformation. In more basic media, such as THF or dioxane, the conversion is very slow.

The halo compounds are of limited stability and are best used directly for subsequent transformations. It was possible, however, to purify chloro derivative 2a (X=Cl) by rapid chromatography.



(a) R_1 =  , $R_2 = NH_2$, $R_3 = OCH_3$ (b) $R_1 = (CH_2)_3$-CH(NH-$COOCH_2CCl_3$)-$COOCH\phi_2$, $R_2 = NH_2$, $R_3 = OCH_3$

(c) R_1 =  , $R_2 = CH_3$, $R_3 = H$ (d) $R_1 = (CH_2)_3$-CH(NH_2)-COOH, $R_3 = OCH_3$

X = Cl, Br, I

Y = CN, N_3, H, OCH_3, OH

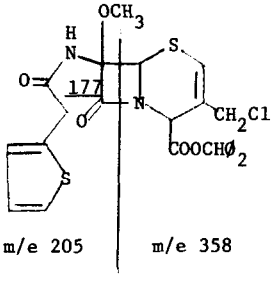
The halo compounds were easily converted to azido[6] (3a, Y=N_3), cyano[9] (3b, Y=CN), methoxy[10] (3a, Y=CH_3O) and hydroxy[6] (3b, Y=OH) derivatives by the known procedures.

Since most of the intermediates mentioned above refused to crystallize, purification was effected by chromatography and identifications were based on spectral data.

The NMR spectra of these compounds was similar to that of the known cephalosporins[11]. The C_{10} protons appeared to be an AB system (J_{AB}=10 Hz) which, depending on the relative chemical shifts, showed a broad line or four lines.

Chemical Shifts of the C_{10} Protons (δ) in $CDCl_3$		
1a or 1b	X = $OCONH_2$	4.55 (s)
2a	X = Cl	4.10 (q)
2b	X = Br	4.07 (q)
2b	X = I	4.03 (q)
3b	X = OH	4.07 (s)
3a	X = N_3	3.88 (s)
3a	X = OCH_3	3.83 (q)
3b	X = CN	3.17 (s)

Mass spectroscopy was also a useful tool in the identification of these compounds. The thienyl derivatives (2a, 2c, 3a) gave particularly informative fragmentations, according to the pattern shown:



Compound 3a (Y=OCH_3), after the usual oxidative-reductive double bond isomerization[12] and deblocking, afforded a new active antibiotic 4a (Y=OCH_3):UV max (pH 7 buffer) 2600 nm (ε 7800), 2360 nm (ε 12500); NMR (CD_3CN)δ 3.22 (s, C_{10}-OCH_3), 3.45 (m, S-CH_2), 3.48 (s, C_7-OCH_3), 3.85 (s, CO-CH_2), 4.25 (q, CH_2O), 5.06 (s, C_6-H), 6.8-7.5 (m, C_4H_3S).

References:

(1a) E. O. Stapley, D. Hendlin, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, H. B. Woodruff, T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter, F. J. Wolf, G. Albers-Schonberg, B. H. Arison, and J. L. Smith, 11th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N. J. (1971) Abstract No. 15.

(1b) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehm, W. M. Stark, and J. G. Whitney, J. Amer. Chem. Soc., 93, 2308 (1971).

(2) Previous papers in this series: S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng, and M. Sletzinger, J. Amer. Chem. Soc., 94, 1410 (1972).

(3) The awkward wordiness of describing chemical transformations taking place on the carbon atom attached to the C_3-carbon of the ring system suggests resurrecting the C_{10}-designation used by Newton and Abraham. See for example: G. G. F. Newton, E. P. Abraham, and S. Kuwabara, Antimicrob. Ag. Chemoter., 449, (1967).

(4a) 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).

(4b) J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall and A. G. Long, J. Chem. Soc., 1142 (1966).

(5) For a comprehensive review on C_{10} substitution see: E. H. Flynn, "Cephalosporins and Penicillins," Academic Press, New York, 1972, p. 151.

(6) J. A. Webber and E. Van Heyningen, U. S. Patent 3,637,678 (1972).

(7) J. A. Webber, E. M. Van Heyningen, R. T. Vasileff, J. Amer. Chem. Soc., 91, 5674 (1969).

(8) The NBS bromination method cannot be used with thiophene or furane derivatives since these functions undergo rapid bromination. See reference 6.

(9) J. A. Webber and R. T. Vasileff, J. Med. Chem., 14, 1136 (1971).

(10) J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W. Ryan, E. M. Van Heyningen and R. T. Vasileff, J. Med. Chem., 14, 113 (1971).

(11) G. F. H. Green, J. E. Page and S. E. Staniforth, J. Chem. Soc., 1595 (1965).

(12) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright and E. M. Van Heyningen, J. Org. Chem., 35, 2430 (1970).