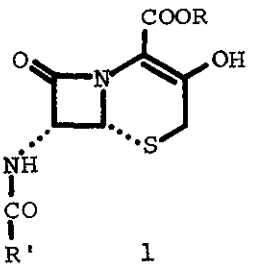
SYNTHESIS OF 3-HYDROXY CEPHEMS

Hans Rudolf Pfaendler, Phillip Andrew Rossy,
Jacques Gosteli, and Robert Burns Woodward

Woodward Research Institute, 4002 Basel, Switzerland

The compounds 2, readily produced from natural penicillin V, are converted to 3-hydroxy cephems 1 through an efficient three-step reaction sequence.

3-Hydroxy cephem esters 1 have gained considerable interest since they were first produced from natural cephalosporins (1), (2).



1

R removable group

R' $PhCH_2$, $PhOCH_2$, etc.

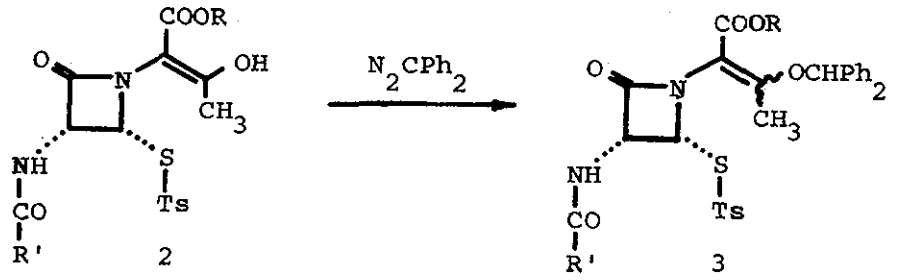
Not suitable themselves as antibiotics, they contain an enol function that represents a structural feature allowing the preparation of novel cephem derivatives (2), (3). Certain of these display high antibiotic potency. The production of

1, consequently, from naturally occurring penicillins as an economical base has been the independent task of research groups in Europe, Japan and the United States.

Some recent solutions to this synthetic problem were presented in lectures at the Symposium of the Chemical Society (London) on "Recent Advances in the Chemistry of β-Lactam Antibiotics" at Cambridge, England (4), (5). These lectures prompt us to disclose some of the results achieved at the Woodward Research Institute.

The important intermediate 2 in one of our routes to 3-alkoxy cephems from penicillins (6) can be used to prepare the target compounds. Since 2 was not readily cyclized directly to 1, a protecting reagent for the enol 2 was devised, such that in a final reaction step the enol function could be liberated to produce the 3-hydroxy cephems 1.

Thus, etherification of 2 was effected by an excess of diphenyldiazomethane in the minimum amount of dioxane. After 14 hr at 60°C a mixture (1:1) of the E and Z isomeric enol benzhydrylethers 3 was isolated in about 90% yield by chromatography [1].

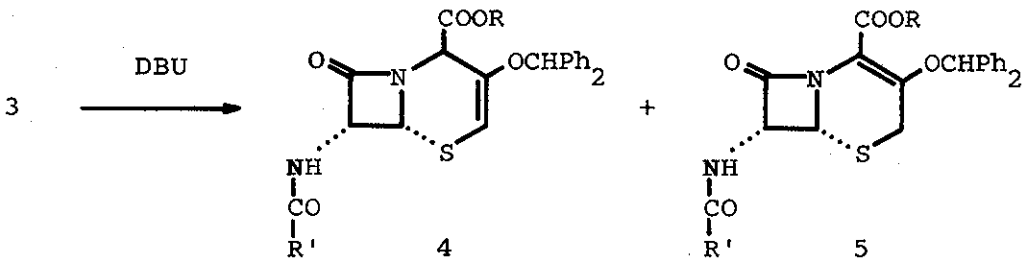


R benzyl, p-nitrobenzyl R' $PhOCH_2$

Ts p-toluenesulfonyl

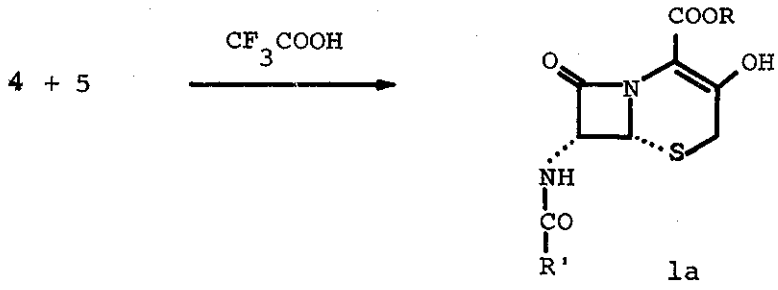
1 Correct analytical and spectroscopic data (ir, nmr, uv) were obtained for all compounds mentioned.

Cyclization with concomitant elimination of p-toluenesulfinic acid occurred with both isomers 3 on treatment with 1.2 equivalents of 1,5-diazabicyclo [5.4.0] undec-5-ene in tetrahydrofuran during 45 min at room temperature (6). Work-up with aqueous acid, followed by sodium bicarbonate treatment gave a mixture of the two cyclic enol ethers 4 and 5 in a 3:1 ratio, respectively. After additional chromatographic purification the yield was 75 to 80%. Although isomers 4 and 5 can be separated by extensive silica gel chromatography their mixture was used for further transformation.



R benzyl, p-nitrobenzyl R' $PhOCH_2$

The two enol ethers 4 and 5 were converted into the expected 3-hydroxy cephem esters 1a in yields of up to 92% when they were treated for 40 min with a 5% solution of trifluoroacetic acid in methylene chloride at room temperature.



R benzyl, p-nitrobenzyl R' $PhOCH_2$

The following physical data, obtained on the pure 3-hydroxy cephem p-nitrobenzyl ester 1a, are typical:

uv (ethanol)	269 nm (14200)
ir (KBr)	2.95, 5.64, 5.97, 6.25, 6.58, 7.42, 13.35, 13.60 μ
nmr ($CDCl_3$) (δ, ppm)	3.40 (2H, ABq, J = 17 Hz) 4.57 (2H, s) 5.05 (1H, d, J = 5 Hz) 5.35 (2H, ABq, J = 14 Hz) 5.70 (1H, dd, J = 5, 10 Hz) 6.6 - 8.4 (10H, m) 11.40 (1H, broad s)
mass	485 (M^+), 306, 295, 191, 153
$[\alpha]_D^{20}$ ($CHCl_3$; c=1)	+ 105 ± 1°
m.p.	96-99°C (from toluene)

REFERENCES

1. R. Scartazzini and H. Bickel, Helv. Chim.Acta, 57, 1919 (1974).

2. R.R. Chauvette and P.A. Pennington, J. Amer. Chem. Soc., 96, 4986 (1974).

3. (a) R. Scartazzini, P. Schneider and H. Bickel, Helv. Chim. Acta, 58, 2437 (1975); (b) unpublished results of the Woodward Research Institute.

4. S. Kukolja, "Synthesis of 3-Methylenecepham, a Key and General Intermediate in the Preparation of 3-Substituted Cephalosporins" (Lecture presented at the Symposium of the Chemical Society (London) at Cambridge, England (June 1976)).

5. T. Tsuji, Y. Hamashima, M. Yoshioka, M. Narisada, Y. Nishitani, K. Minami, H. Ishitobi, K. Ishikura, H. Itani, T. Kubota, M. Murakami, T. Okada, H. Onoue, H. Satoh, Y. Sendo and W. Nagata, "New Conversion of Penicillins into 3-Hydroxycephems" (Lecture presented by T. Tsuji at the Symposium of the Chemical Society (London) at Cambridge, England (June 1976)).

6. (a) CIBA-GEIGY Ltd., German Pat. Publication No. 2506330, Priority Claim Feb. 26, 1974; (b) R.B. Woodward,"Recent Advances in the Chemistry of Natural Products"(Lecture presented at the Fourth International Symposium of the Chemical Society (London) on Synthesis in Organic Chemistry at Cambridge, England (July 1975)); (c) J. Gosteli, Chimia, 30, 13 (1976).

Received, 3rd August, 1976