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A NEW NONAQUEOUS HYDROXYLATING PROCEDURE; THE DIRECT CONVERSION OF PENICILLIN TO DESACETYL CEPHEM

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Recently, Kukolja and coworkers have reported a conversion of penicillin sulfoxide, 1, to 3-exomethylene cepham sulfoxide, 2.[1] Subsequently, we described a procedure for converting 2 to the 3-bromomethylcephem, 3a, by trapping the allylic anion with halogen.[2] We have demonstrated that 3 undergoes ready displacement with nucleophiles such as acetate ion and various heteroaromatic thiols.[2,3]

Cefoxitin, 3e, is currently being evaluated clinically. Heretofore, there have been no reports of a direct conversion of penicillin to 3e. The cephem, 3a, appeared to be a potentially useful substrate for its conversion to the cephem having the carbamoyloxymethyl functionality at C_3. However, attempts to displace with the carbamate anion had been unsuccessful.[2,4]

An alternate method would be simple hydrolysis of 3a to 3b and conversion to carbamate by standard methods. However, 3a is resistant to hydrolysis under mild conditions and undergoes β-lactam decomposition under more vigorous conditions. We would like to disclose a new nonaqueous hydroxylating procedure that has been utilized in converting 3a to desacetylcephem, 4b.

Treatment of 3a with 1 eq of sodium γ-hydroxybutyrate in hexamethylphosphoric triamide afforded upon workup and preparative chromatography a 65% yield of 4a[5,6] isolated as a foam; ir ($CDCl_3$) (1775, 1745, 1710) cm^{-1}; nmr ($CDCl_3$) δ 1.7-2.6 (m, 4, $OCOCH_2CH_2CH_2OH$), 3.55 (m, 2, CH_2OH), 3.83 (s, 2, side chain CH_2), 4.63 (bs, 1, $-CH_2OH$), 5.0 (s, 1, C_4-H), 5.23 (d, 1, J=4 Hz, C_6-H), 5.58 (dd, 1, J=4 and 8 Hz, C_7-H), 6.42 (bs, 1, C_2-H), 6.95 (s, 1, ester CH), and 7.36 (m, 13, thienyl + ArH).

The γ-hydroxybutyrate ester was subsequently cleaved by the reaction of 4a with trifluoroacetic acid (TFA) in methylene chloride (CH_2Cl_2), 10^{-4}M TFA in CH_2Cl_2 for 6 hr at 0°C. Workup of the reaction mixture followed by quick column chromatography afforded a 75% yield of 4b; ir (1775, 1750, 1710) cm^{-1}; nmr (acetone D-6) δ 3.85 (s, 2, side chain CH_2), 4.17 (s, 2, $-CH_2OH$), 5.25 (d, 1, J=4.5 Hz, C_6-H), 5.54 (dd, 1, J=4.5 and 8.0 Hz, C_7-H), 6.40 (bs, 1, C_2-H), 6.95 (s, 1, ester CH), 7.32 (m, 13, thienyl + ArH), and 8.04 (d, 1, J=8.0 Hz, side chain NH).[7,8,9]

The conversion to cefoxitin, 3e, was completed by the following sequence. Treatment of 4b with trichloroacetylisocyanate followed by solvolysis with methanol and potassium carbonate afforded 4c.[10] This was converted to 3c with m-chloroperbenzoic acid in isopropanol-methylene chloride and reduction of the cephem sulfoxide with phosphorous trichloride in dimethylacetamide.[11] Methoxylation of 3c with lithium methoxide and (t)butylhypochlorite in tetrahydrofuran afforded 3d in 60% yield.[12] The removal of the ester protecting group with trifluoroacetic acid gave cefoxitin, 3e.

REFERENCES

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2. G. A. Koppel, M. D. Kinnick, and L. J. Nummy, J. Amer. Chem. Soc., 99, 2822 (1977).
3. G. A. Koppel, Recent Advances in the Chemistry of β-Lactam Antibiotics, Cambridge, England (1976).
4. Netherlands Patent 7,208,855.
5. The reaction affords a 4:1 mixture of 4a and its corresponding Δ^3-cephem isomer.
6. All new compounds gave satisfactory mass spectral and elemental analyses.
7. The corresponding Δ^3-isomer under these conditions lactonizes to the cephalosporin lactone.

8. For a use of levulinate ester as an alcohol protecting group, see A. Hassner, G. Strand, M. Rubinstein, and A. Patchornik, J. Amer. Chem. Soc., 97, 1614 (1975).

9. Cephem 4b was identical to that prepared from 7-ACA.

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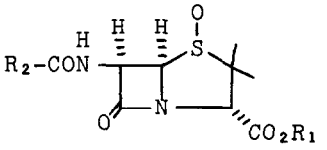

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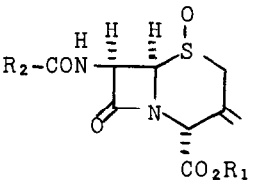

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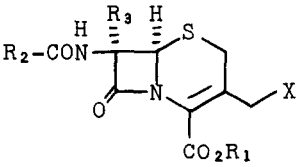
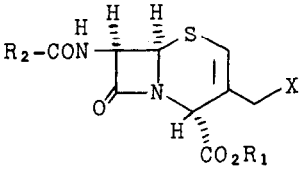


3a: R_1 = benzhydryl, R_2 = thienylmethyl, R_3 = H, X = Br
b: R_1 = benzhydryl, R_2 = thienylmethyl, R_3 = H, X = OH
c: R_1 = benzhydryl, R_2 = thienylmethyl, R_3 = H, X = $OCONH_2$
d: R_1 = benzhydryl, R_2 = thienylmethyl, R_3 = OCH_3, X = $OCONH_2$
e: R_1 = H, R_2 = thienylmethyl, R_3 = OCH_3, X = $OCONH_2$



4a: R_1 = benzhydryl, R_2 = thienylmethyl, X = $OC(=O)CH_2CH_2OH$
b: R_1 = benzhydryl, R_2 = thienylmethyl, X = OH
c: R_1 = benzhydryl, R_2 = thienylmethyl, X = $OCONH_2$