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THE CONVERSION OF DEACETYLCEPHALOSPORIN C TO A DERIVATIVE OF 7-(5-AMINO-5-CARBOXYVALERAMIDO)-3-CARBAMOYLOXYMETHYL-3-CEPHEM-4-CARBOXYLIC ACID

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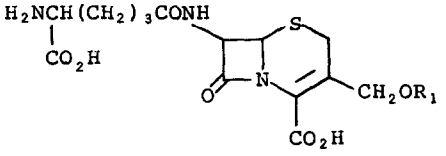
Nagarajan et al.[1] have assigned the structure 7-(5-amino-5-carboxy-valeramido)-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid (1) to a new β-lactam antibiotic produced by a Streptomycetes species. The similarity of 1 to cephalosporin C (2) prompted us to consider the synthesis of a compound derivable from both 1 and 2 to further document the structure of 1.

Impure deacetylcephalosporin C (3) is isolable from either fermentation[2] or enzymatic deacetylation[3] of cephalosporin C. Crude deacetylcephalosporin C was purified[4] by passing it over a neutral polystyrene resin (Amberlite XAD-4) in water at pH 4.



1 $R_1 = CONH_2$

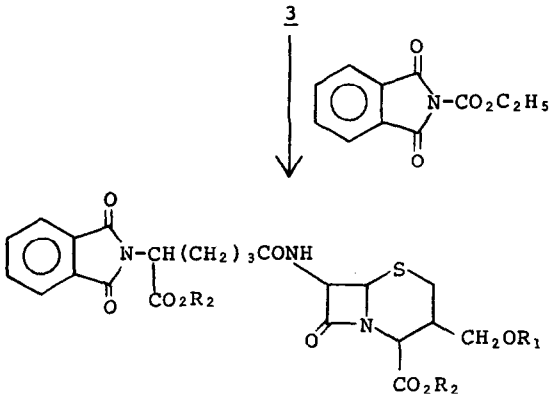
2 $R_1 = COCH_3$

3 $R_1 = H$

N-Carboethoxyphthalimide reacted with 3 in pH 8.5 phosphate buffer to give the phthalimido derivative 4.[5] The dibenzhydryl ester 5 was obtained from the diacid 4 in dioxane with two equivalents of diphenyldiazomethane.[5] Neither 4 nor 5 could be obtained analytically pure because of their facile conversion to lactones.

Trichloroacetylisocyanate[6] reacted with 5 in acetone to give the fully protected derivative 6.[7] The trichloroacetyl group was hydrolyzed during a chromatographic purification of 6 over silica gel:10% H_2O. Elution with ethyl acetate gave a 30% overall yield from 3 of dibenzhydryl 7-(5-phthalimido-5-carboxyvaleramido)-3-carbamoyloxymethyl-3-cephem-4-carboxylate (7). The

trichloroacetyl group can be removed alternatively with a catalytic amount of sodium carbonate in methanol.



4 $R_1 = R_2 = H$

$(Ph)_2CN_2$

5 $R_1 = H$; $R_2 = CH(Ph)_2$

$Cl_3CCONCO$

6 $R_1 = CONHCOCCl_3$; $R_2 = CH(Ph)_2$

H_2O, OH^-

7 $R_1 = CONH_2$; $R_2 = CH(Ph)_2$

1) H^+
2) CH_2N_2

8 $R_1 = CONH_2$; $R_2 = CH_3$

The diester 7 crystallized from cold ethanol (mp 95-101°). Anal. Calcd for $C_{49}H_{42}N_4O_{10}S$: C, 66.96; H, 4.82; N, 6.37. Found: C, 66.70; H, 4.74; N, 6.21.

An nmr spectrum of the N-phthalimido-dibenzhydryl ester derivative of the compound isolated by Nagarajan et al.[1] was identical with that of 7. Important features of the nmr spectrum of 7 in DMSO-d_6 were resonances occurring at 3.58 δ (C_2-H), 4.78 δ (-CH_2OCON), 5.28 δ (C_6-H), 5.75 δ (C_7-H), and 6.65 δ (-CONH_2).

Compound 7 was dissolved in trifluoroacetic acid and anisole at ice temperature for 4 hr to remove the benzhydryl protecting groups. The diacid was re-esterified with diazomethane to give the dimethyl ester 8. The physical properties, mp 149-151°, mixture mp 151-153°; uv (EtOH): λ_{max} 262 (8,000), 219 nm (44,000); ir ($CHCl_3$) 3400, 3250, 3100 (NH), 1780 (β-lactam), 1710 (carbamate carbonyl), 1650, 1655 cm^{-1} (amide); and mass spectra m/e 345.106 (0.5) $C_{17}H_{17}O_6N_2$ (side chain fragment), m/e 213.044 (0.5) $C_8H_{11}O_4N_2S$ (dihydrothiazine fragment), were identical with those of the N-phthalimido-dimethyl ester derivative of 7-(5-amino-5-carboxyvaleramido)-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid prepared by Nagarajan et al.[1]

Anal. Calcd for $C_{25}H_{26}N_4O_{10}S$: C, 52.26; H, 4.56; N, 9.75. Found: C, 52.48; H, 4.40; N, 9.45.

The nmr spectra of the two compounds were also identical with noteworthy resonances (DMSO-d_6) at 3.67, 3.79 δ (2-CO_2CH_3); 5.12 δ (d, J=4.5 Hz) (C_6-H); 5.66 δ (q, J=4.5, 8.5 Hz) (C_7-H); and 7.95 δ (C_6H_4).

These data confirm the proposed structure of 7-(5-amino-5-carboxyvaleramido)-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid.

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