Tetrahedron Letters No. 36, pp 3205 - 3206, 1976. Pergamon Press. Printed in Great Britain.

REACTIONS OF CEPHALOSPORANATES: MICHAEL REACTIONS AT C-4.

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(Received in UK 25 June 1976; accepted for publication 16 July 1976)

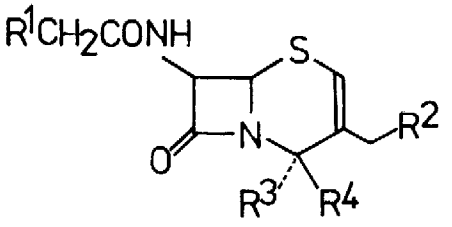
We have recently reported new functionalization reactions at C-2 and C-4 of cephalosporanates and cephalosporanate (R)- and (S)- sulphoxides.[1] Because of the importance of introducing functional groups at these positions[2] we have extended our studies and now show that in mild basic conditions cephalosporanates react exclusively at C-4 with certain Michael acceptors.

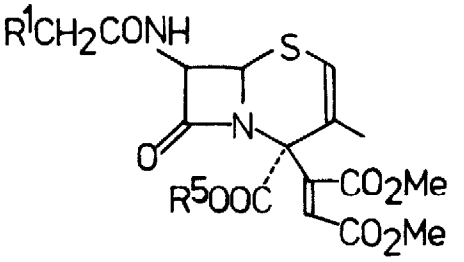
For example, trichloroethyl 7β-phenoxyacetamidodesacetoxycephalosporanate (1) reacted readily in acrylonitrile-triethylamine at room temperature to give the 4-substituted 2-cephem (2) (75%) as an oil, $[\alpha]_D^{22}$ + 255° (c=1.33 in $CHCl_3$) together with a minor isomer (3) (9%), also an oil, $[\alpha]_D^{22}$ + 228° (c=0.71 in $CHCl_3$). The 2-cephem structures were assigned by n.m.r. (δ6.40, q, J=1Hz and 6.46, q, J=1Hz respectively) and by u.v. spectroscopy (λ_{max}, EtOH, 258 and 260 nm respectively). The stereochemistry at C-4 in the major isomer (2) was assigned as shown, i.e. the β-face adduct, by analogy with related alkylations at C-4.[2] [Compound (2) was also prepared by Michael addition of acrylonitrile to the cephalosporanate (R)- sulphoxide,[1] followed by deoxygenation. The (S)- sulphoxide gave the 2α-adduct.[1]] De-esterification of (2) gave the carboxylic acid (60%), m.p. 212-214°, $[\alpha]_D^{22}$ + 315° (c=0.4 in acetone).[4]

Methyl acrylate did not react with (1) under similar conditions, but dimethylbutynedioate in acetonitrile - triethylamine gave (4) (80%), m.p. 143-144°, $[\alpha]_D^{22}$ + 355° (c=0.85 in $CHCl_3$). (δ 6.46, butenedioate proton[5]; λ max, EtOH, 258, 270, 275 nm). Removal of the trichloroethyl group[3] led, not to a carboxylic acid or to a spiro-γ-lactone but to decarboxylation and formation of four isomeric β-lactam products the structures of which are under investigation.

It was of obvious importance to ascertain the effect of a typical 3-substituent on the Michael reaction. The diphenylmethyl ester of cephalothin was therefore treated with acrylonitrile-triethylamine, giving (5) (87%) as an oil, $[\alpha]_D^{22}$ + 230° (c=1.52 in $CHCl_3$). A C-4 isomer (6) (10%), $[\alpha]_D^{22}$ + 232° (c=0.65 in $CHCl_3$) with closely similar spectroscopic characteristics was also isolated as an oil.

These preliminary observations, together with related alkylation studies[1,2] extend the present knowledge[6] of the modes of alkylation of cephalosporanates, and provide adducts which may be of use in the synthesis of structurally-modified β-lactam antibiotics.





2, $R^1 = Ph$, $R^2 = H$, $R^3 = (CH_2)_2CN$ 4, $R^5 = CH_2CCl_3$
$R^4 = CO_2CH_2CCl_3$

3, $R^1 = Ph$, $R^2 = H$, $R^3 = CO_2CH_2CCl_3$
$R^4 = (CH_2)_2CN$

5, $R^1 =$  , $R^2 = OAc$,
$R^3 = (CH_2)_2CN$, $R^4 = CO_2CH_2CCl_3$

6, $R^1 =$  , $R^2 = OAc$,
$R^3 = CO_2CH_2CCl_3$, $R^4 = (CH_2)_2CN$

Acknowledgements We are grateful to Pfizer Central Research for a gift of starting materials, and to S.R.C. for a studentship to D.H.B.

All new compounds were fully characterized spectroscopically exhibited correct elemental analysis and/or molecular ion high resolution mass measurement.

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