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CYCLOADDITION REACTIONS OF VINYLCEPHALOSPORINS WITH DIAZOALKANES[1]

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Summary: In the reaction of a vinylcephalosporin (2) with diazoalkanes the initially formed 3-pyrazolinocephalosporins (3) underwent further reactions leading either to bispyrazolinocephalosporins (5) or to cyclopropylcephalosporins (6).

1,3-Dipolar cycloaddition is a widely used method for modifications of β-lactam antibiotics[2-4], however, it was applied only in a few cases[5] for transformations of cephalosporins at position 3.

Cephalosporins containing a heterocycle attached directly to the dihydrothiazine moiety are potential antibacterial agents because of their interesting chemical and biological feature[5c,6]. For this reason we decided to prepare such type of compounds.

The starting material, a 3-vinylcephalosporin (2) (Scheme) - derived from 7-aminocephalosporanic acid[7] (1) -contains a vinyl group in a conjugated system, offering new possibilities for the preparation of novel 3-substituted cephalosporins.

In the reaction of 2 with diazomethane our expectations were:

1, after a few minutes reaction time only one or two products form with diazomethane by an α- and/or β-face attack on the vinyl group,

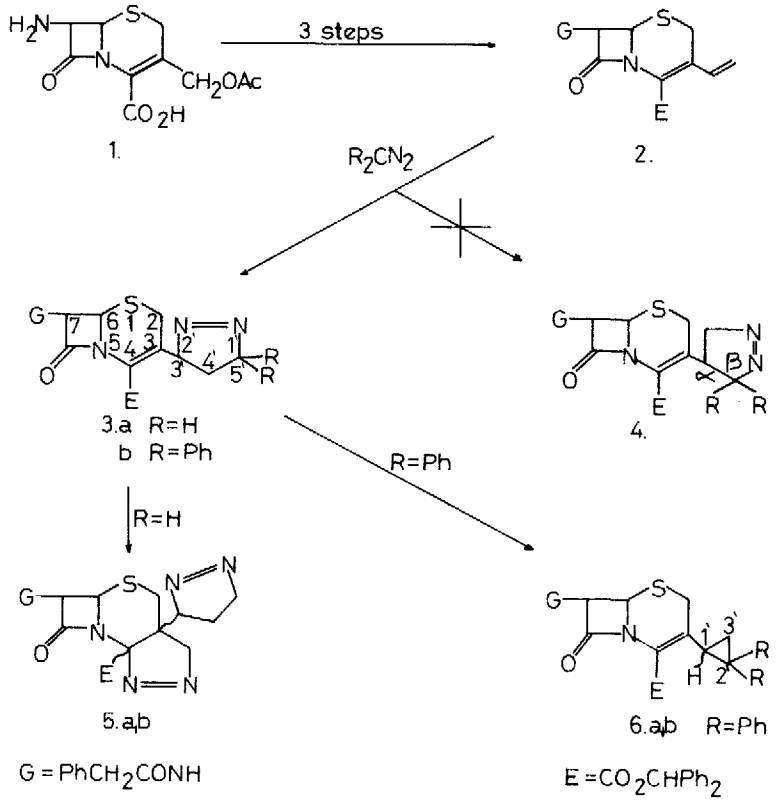
2, based on the FMO-theory[8] the products are "β-adducts" (3), i.e. the new carbon-carbon bond forms at β-position to carbon C-3,

3, the Δ^3 double bond of cephalosporins is unreactive under such conditions.

When compound 2 and a large excess of diazomethane were allowed to react at room temperature in dichloromethane there was only a single product after 5 minutes, but before completion of the reaction the formation of two additional products, a major and a minor one was observed. Based on the ^1H and ^{13}C NMR spectra[9] the structure of the initially formed main product is 3a. The ^1H and ^{13}C NMR spectra[10] of the other major product (5a) are similar to those of 3a, but both suggest the presence of a new $-CH_2-$ signal characteristic of 3,4-pyrazolinocefams[3]. The ^1H NMR spectrum[11] of the

minor product (5b) produced in a very small quantity is closely related to that of 5a indicating that these two compounds are probably different only in the configurations at C-3 and C-4.

On the basis of these findings it is concluded that the reaction of 2 with diazomethane leads to the regio- and stereospecific formation of a 3-pyrazolinocephalosporin (3a), which then undergoes a further conversion with the excess diazomethane to give bis-adducts of type 5. This latter is



1. 2. 3.a R=H b R=Ph 4. 5.a,b 6.a,b R=Ph

Scheme

quite surprising in the light of our earlier findings[3b] that the Δ^3 double bond of cephalosporins is rather unreactive towards diazomethane.

When the 1,3-dipolar cycloaddition was carried out with diphenyldiazomethane, vinylcephalosporin 2 was found to be unexpectedly unreactive at room temperature, and the reaction was completed only after refluxing in dichloromethane for 40 hours. Surprisingly, the reaction with this bulky

diazomethane gave two products: the two C-3' enantiomers in a ratio of 2:1 (NMR). Based on ^{1}H and ^{13}C NMR data[12] these products are cyclopropanes (6a,b), i.e. upon heating the initially formed pyrazolines (probably β-adducts of type 3) undergo a decomposition reaction[2,4] involving nitrogen elimination. The Δ^{3} double bond remained unaffected in this reaction.

The details of chemistry, biology and structure elucidation of the products will be described in a separate communication.

References and notes

1. Cycloaddition Reactions of Cephalosporin Compounds. XII. Part XI. ref. 4b
2. See for example:
   a, J.H. Bateson, D.F. Corbett, and R. Southgate, in "Recent Advances in the Chemistry of β-Lactam Antibiotics", (A.G. Brown, S.M. Roberts, Eds.), The Royal Society of Chemistry, Spec. Publ. No 52, London, 1985, pp. 116-130.
   b, K.S.K. Murthy and A. Hassner, Tetrahedron Lett., 28, 97 (1987)
3. a, R.A. Archer and B.S. Kitchell, J. Org. Chem., 31, 3409 (1966).
   b, E.R. Farkas, E.T. Gunda, and J.Cs. Jászberényi Tetrahedron Lett., 5127 (1973)
   c, T.E. Gunda, H. Hakli, and J.Cs. Jászberényi, Acta Chem. Scand., B. 37, 31 (1983)
4. a, J.Cs. Jászberényi, K.E. Kövér, Org. Magn. Reson., 22, 552 (1984)
   b, J. Pitlik and J.Cs. Jászberényi, J. Heterocyclic Chem., in press
   c, J.Cs. Jászberényi, J. Pitlik, Gy. Batta, K.E. Kövér, and K. Kollár, Magn. Reson. Chem., 26, 658 (1988)
5. a, D. Willner, A.M. Jelenevsky, and L.C. Cheney, J. Med. Chem., 15, 948 (1972)
   b, D.O. Spry, J. Org. Chem., 40, 2411 (1975)
   c, J.L. Fahey, R.A. Firestone, and B.G. Christensen, J. Med. Chem., 19, 562 (1976)
6. R.A. Firestone, N.S. Maciejewicz, and B.G. Christensen, J. Org. Chem., 39, 3384 (1974)
7. a, J.C. Clark, J. Kennedy, A.G. Long, and N.G. Weir (Glaxo Ltd.,), Ger Offen., 2 103014; Chem. Abstr. 75, 118328 (1971)
   b, H. Yamanaka, T. Chiba, K. Kawabata, H. Takasugi, T. Masugi, and T. Takaya, J. Antibiot., 38, 1738 (1985)

8. I. Fleming, Frontier Orbitals and Organic Reactions, Wiley, London, 1976

9. Selected spectral data for 3a (mp.: 104-107°):
^{1}H NMR (DMSO-d_6, ppm): 1.2 and 1.8 (m, 4'-CH_2); 4.1 and 4.8 (m, 5'-CH_2); 5.05 (t, 3'-CH). Couplings are observed between the C-4' and C-5' protons showing that they are not separated by the N=N bond (i.e. the molecule is not an "α-adduct" of type 4).
^{13}C NMR (DMSO-d_6, J-echo, ppm): 22.516 (C-4'-CH_2); 76.670 (C-5'-CH_2); 87.677 (C-3'-CH). These data show that C-4' is in the region of C-C bonds while C-5' and C-3' is in that of C-N bonds, exhibiting that this compound is not a cyclopropane derivative and not "α-adduct".
Ms (CI) (m/z; %): 553 (M^++1; 9%)

10. Selected spectral data for 5a (mp.: 111-115°):
^{1}H NMR (DMSO-d_6, ppm): 0.9 and 1.6 (m, 4'-CH_2); 3.9 and 4.75 (m, 5'-CH_2) 4.2 (m, 3'-CH) and 4.75 (ABq, pyr-CH_2)
^{13}C NMR (DMSOd_6, J-echo, ppm): 19.761 (C-4'-CH_2); 46.825 (C-3-quat.); 76.855 (C-5'-CH_2); 87.886 (pyr-CH_2); 90.631 (C-3'-CH); 104.873 (C-4-quat.)
Ms (EI) (m/z; %): 566 (M^+-28; 6%)

11. Selected ^{1}H NMR data for 5b (DMSO-d_6, ppm): 1.1 and 2.2 (m, 4'-CH_2); 4.0 and 4.75 (m, 5'-CH_2); 4.7 (m, 3'-CH); 5.2 (ABq, pyr-CH_2)

12. Selected spectral data for 6a and 6b (mp.: 87-90°):
major product (6a):
^{1}H NMR ($CDCl_3$, ppm): 1.42 and 1.48 (t, 3'-CH_2); 3.76 (t, 1'-CH)
^{13}C NMR (DMSO-d_6, ppm): 18.824 (C-3'-CH_2); 26.308 (C-2'-quat.); 27.566 (C-1'-CH)
minor product (6b):
^{1}H NMR ($CDCl_3$, ppm): 1.38 and 1.66 (t, 3'-CH_2); 2.91 (t, 1'-CH)
^{13}C NMR (DMSO-d_6, ppm): 18.824 (C-3'-CH_2); 26.308 (C-2'-quat.); 28.700 (C-1'-CH)
Ms (EI) (m/z; %): 676 (M^+; 8%)

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