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STUDIES RELATED TO CEPHALOSPORINS.IV. ELECTROPHILIC ADDITION TO 3-EXOMETHYLENE-1-CEPHAMS. THE ADDITION OF PHENYLSELENENYL CHLORIDE.

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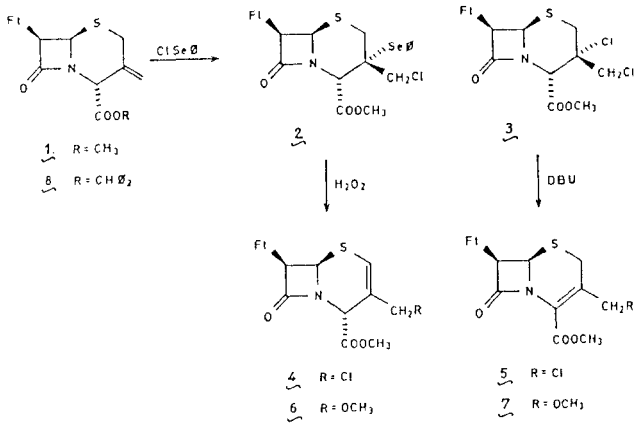
Abstract: Phenylselenenyl chloride addition to the 3-exomethylene-1-cepham 1 gave mainly the seleno derivative 2 at room temperature while the dichloro derivative 3 was obtained in refluxing 1,2-dichloroethane. Compounds 2 and 3 transformed into the Δ_2 and Δ_3 chloromethyl isomer respectively.

Electrophilic additions of sulphenyl chlorides to 3-exomethylene-1-tiacephams have been already described[1,2]. As far as the regiochemistry of the addition is concerned,the most recent results[1] are discordant from the previous findings[2].To the best of our knowledge no reports are available on the addition of selenenyl chlorides to these compounds.Our interest in the functionalization of cephalosporins at C-3'[3], prompted us to study extensively electrophilic additions to these substrates: the results obtained by using phenylselenenyl chloride as reagent are reported in this communication.

Substrate 1 was reacted in the dark for 10 hr with an excess of phenyl selenenyl chloride[4] in CCl_4 at room temperature.HPLC separation of the reaction mixture afforded 3α-selenophenyl-3β-chloromethyl cepham 2 in a yield of 87%. 3α-Chloro-3β-chloromethyl cepham 3 was obtained as by product. The regiochemistry of the reaction affording 2 was suggested by the presence of a double doublet centered at δ 3.65 and 4.00 in the ^{1}H NMR spectrum of 2, assigned to the chloromethyl group at C-3. In addition compound 2 did not dehydroalogenate when treated with DBU, as 3-chloromethyl derivatives do under

such conditions[5]. Furthermore, the ^{1}H NMR spectrum of 2 showed a singlet (2H) at δ 5.50 which was assigned to the C-6 and C-7 protons. The overlap of these signals was attributed to a deshielding effect on the C-6α proton: an α-stereochemistry of the phenylseleno group was therefore supposed. Chemical evidence of this stereochemical feature was obtained by the oxidative-elimination[6] of the phenylseleno moiety in 2 which afforded methyl 7-phtalimido-3-chloro-2-cephem-4-carboxilate 4 as the sole product (yield 44%). When 4 was trapped by reacting the crude reaction mixture whith methanol, the methoxy derivative 6 was obtained in a yield of 86%.Its structure was confirmed by comparison with an authentic sample available in our laboratory. The dichlorocepham 3 was dehydroalogenated with DBU and afforded 5 in quantitative yield. The chloromethyl-2-cephem 5 was converted with methanol into the methoxy derivative 7 and compared with an authentic sample. The α-stereochemistry of the chloride at C-3 was established by comparison of its ^{1}H NMR spectrum with that of methyl 3α-bromo-3β-bromomethyl-7-phtalimido-cepham-4-carboxylate, whose structure was unambiguosly determined by X-ray crystallography [7].



When the phenylselenenyl chloride addition was carried out at higher reaction temperature (refluxing 1,2-dichloroethane)[8] with an excess of the reagent (3 moles equivalent) products 2 and 3 were obtained in approximately reversed yields (6% and 81%, respectively). The presence of 3 could not be abscribed to the chlorine hypothetically present in the reaction mixture, as

shown by the fact that a reaction performed with Cl_2 in the same experimental conditions gave a complex mixture of products. On the other hand the seleno derivative 2 was not an intermediate along the path affording 3 since it was recovered unchanged when refluxed whith phenylselenenylchloride in 1,2-dichloroethane. In addition the reaction rate was not affected by the presence of the radical inhibitor 2,6-ditert-butyl-p-cresol.

The unexpected formation of the dichloro derivative 3, having the same stereochemistry at C-3 as product 2 could be explained as follows. Episelenonium ions initially formed by electrophilic attack of the reagent on the double bond can have an α or a β stereochemistry. The α-isomer suffers successive nucleophilic attack at C-3' (less hindered side) giving product 2. The β isomer, being the α-face less hindered than the β-one, suffers the nucleophilic attack at C-3,according to the Markovnikov rule,and the α-chloride at C-3 is generated. However, in this case phenylseleno group at C-3'(a primary carbon atom)is readily displaced by the excess of the reagent[9] and the dichloro derivative 3 is produced. The different results obtained at different reaction temperatures can be explained assuming[10] a thermodynamic control in the reaction carried out in refluxing 1,2-dichloroethane.

It seems likely that the different results recorded in the literature[1,2] on this argument mainly depend on the steric hindrance of the carboxylate ester at C-4. When the ester is bulky (i.e.benzydryl esters[1]), the attack is preferentially β, whereas for less bulky esters (i.e.methyl esters[2]) the attack can be either α or β. Evidence of the decisive role played by the hyndrance of the carboxylate ester is given by the unreactivity of 8, prepared through the Kukolja procedure[11], towards phenylselenenyl chloride addition, even in refluxing 1,2-dichloroethane.

The reaction described here represents also an useful pathwahy to prepare 3-chloromethyl-2-cephem and 3-chloromethyl-3-cephem derivatives starting from a common precursor, easily available through the Kukolja enlargement procedure of penicillin[11].

Acknowledgements

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References and footnotes

1) T. Aoki, T. Koinoke, H. Itami, T. Tsuji, M. Yoshioka, and W. Nagata, Tetrahedron, 39, 2515 (1983). 2) H. Yamaguchy, I. Terai, K. Ozawa, T. Oba, S. Yshimoto, (Tejin LTD) Japan Kokai 7759, 185 C.A.87, 152240m (1977). M. Foglio, G. Franceschi, (Società Farmaceutica Italiana SPA) Belg. 860, 783. C.A. 89, 109542s (1978).

3) F. Animati, M. Botta, F. De Angelis, A. Dorigo, I. Grgurina,and R. Nicoletti J. Chem. Soc. Perkin I, 2281 (1983); M. Botta, F. De Angelis, I. Grgurina, M. Marzi, and R. Nicoletti, J. Het. Chem.,22, 1001 (1984); F. De Angelis, M. Botta, F. Giannessi, and R. Nicoletti, "Recent Advances in the Chemistry of β-Lactam Antibiotics", Proc. 3nd International Symposium, Cambridge (U.K.), 1984, A.G. Brown and S.M. Roberts Ed., p.331. Special Publication, The Royal Society of Chemistry, London, 1985.

4) With 1.1 equivalent of phenylselenenyl chloride in the same experimental conditions it was too slow to be of synthetic utility.

5) L. De Ferra, Doctorate Thesis, University of Rome, 1983.

6) A syn elimination of phenylselenic acid has been reported: K.B. Sharpless, R.F. Lawer, and M. Young, Tetrahedron Lett.,22, 1979 (1973).

7) M. Botta, F. De Angelis, and R. Nicoletti, unpublished results.

8) The same reaction at room temperature gave almost exclusively product 2.

9) Examples of phenylseleno group displacement have been already reported: A.M. Morella, and A.D. Ward, Tetrahedron Lett.,25, 1197 (1984), and literature therein cited.

10) Phenylselenenyl chloride addition is reported to add reversibly to terminal olefins see: L. Engman, Tetrahedron Lett., 28, 1463 (1987) and literature therein cited.

11) S. Kukolja, S.R. Lammert, M.R.B. Gleissner, and A.I. Ellis, J. Amer. Chem. Soc.,98, 5004 (1976).

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