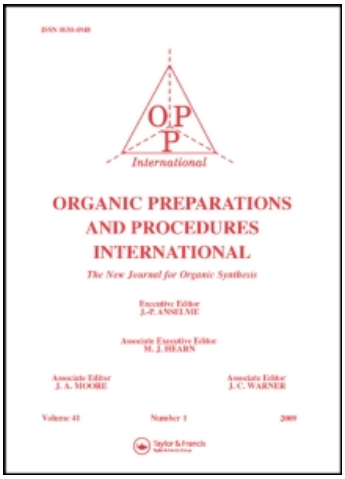

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NEW SELECTIVE SYNTHESIS OF 3-BROMOMETHYL-3-CEPHEM ESTERS

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NEW SELECTIVE SYNTHESIS OF 3-BROMOMETHYL-3-CEPHEM ESTERS

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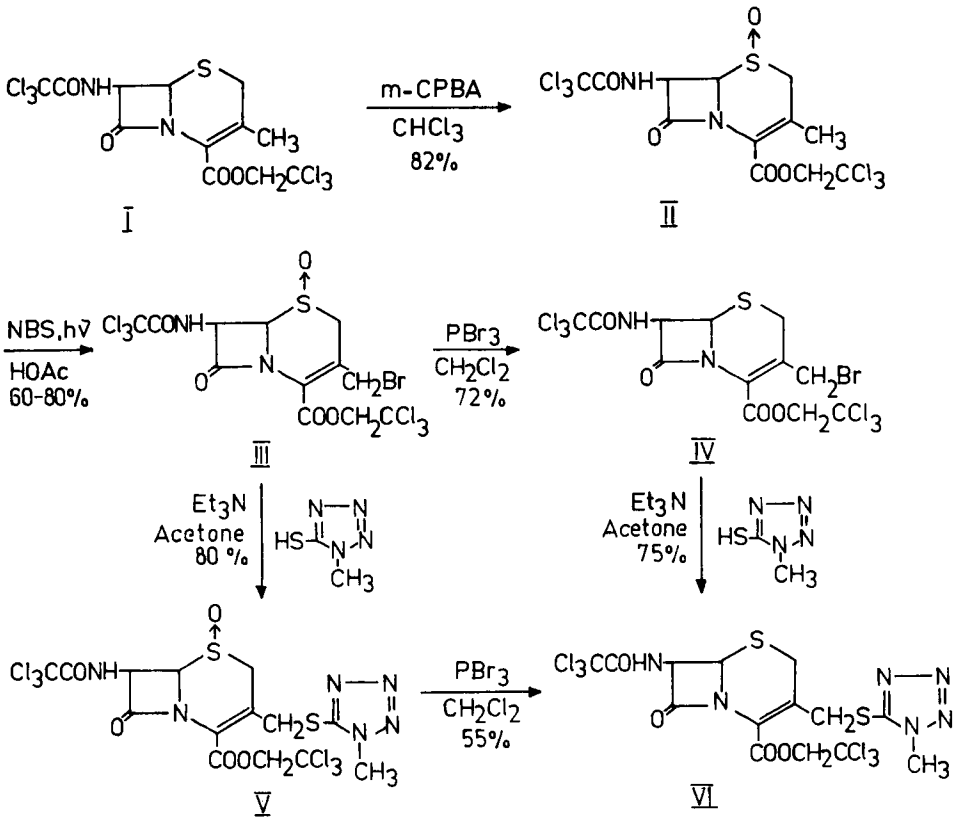
7-Acylamido-3-halomethyl-3-cephem-4-carboxylic acid esters are potential intermediates for the preparation of the modern, second and third generation cephalosporin molecules. These compounds are generally snythesized by the halogenation of secopenicillins[2], deacetoxy-cephem-, deacetyl-cephem-,[3,4] 3-acetoxymethyl-cephem-,[5,6] or 3-exo-methylene-cepham[1] derivatives. The most common method for the halogenation[7-9] involves the bromination of 2-cephem esters with N-bromosuccinimide. The patent literature describes several procedures[10-13] for the photocatalytic halogenation of 3-methyl-3-cephem 1-oxide esters using N-chloro- or N-bromosuccinimide, N-bromoacetamide, N-chlorophthalimide, 1,3-dibromo-5,5-dimethylhydantion or N-bromocaprolactam. However, most of the above methods for the halogenation at C-3' are not selective enough, leading to the undesired substitution[11,12] of the C-2 carbon atom, the 7-acylamido side-chain and of the ester group.

Recently, Japanese authors[13] have reported an efficient and highly selective method for the bromination of 2',2',2'-

trichloroethyl-7-phenylacetamido-3-methyl-3-cephem-4-carboxylate 1-oxide with N-bromosuccinimide (AcOH, 20°C, hν, under nitrogen atmosphere). In our hands, this reaction using the reported conditions gave a mixture of five products (detected by tlc) from which three crystalline compounds, 2',2',2'-trichloroethyl-7-phenylacetamido-3-bromomethyl-3-cephem-4-carboxylate 1-oxide, its 7-D-α-bromo- and 7-L-α-bromo analogues could be separated by column chromatography (Silicagel G, 10:1 dichloromethane-acetone). The structure of the above products was established by ^{1}H-NMR. The remaining two components, formed in traces, could not be isolated. Although this bromination is not selective, the great adavantage of this method is that the undesired C-2 derivative forms at most in a very slight extent.

We felt that the bromination reaction of a cephalosporin molecule, having a strong electron-withdrawing ester group and 7-acylamido side-chain, might be even more selective and would yield predominantly the desired C-3'-bromo compound. In order to prove this assumption, 2',2',2'-trichloroethyl-7-trichloroacetamido-3-methyl-3-cephem-4-carboxylate 1-oxide (II) was prepared in excellent yield by the oxidation of the known 2',2',2'-trichloroethyl-7-trichloroacetamido-3-methyl-3-cephem-4-carboxylate (I)[14,15] with m-chloroperbenzoic acid in chloroform. The product II spontaneously crystallized from the reaction mixture.

Bromination of II was carried out with N-bromosuccinimide in glacial acetic acid with exposure to UV light and



the product, 2',2',2'-trichloro-ethyl-7-trichloroacetamido-3-bromomethyl-3-cephem-4-carboxylate 1-oxide (III) precipitated from the reaction mixture in good yield (61 %). Work up of the mother liquor containing compound III exclusively, increased the yield up to 80 %. Compound III is easily crystallizable and can be stored for several months at room temperature without decomposition.

The selective formation of III from II could be unequivocally established by the comparison of their ^{1}H-NMR-spectra. The characteristic signal of the C-3 methyl group of II at

2.15 ppm (s, 3H) did not appear in the spectrum of III, which, as expected, contained a singlet at 4.59 ppm (2H), assignable to the CH_2Br methylene group. The exactness of the $C_{12}H_9BrCl_6N_2O_5S$ formula proposed for III was also proved by mass spectral investigations. Besides the most characteristic fragmentations, the isotope distribution of the molecular ions was in good agreement with the presence of the six chlorine and one bromine atoms expected from the above formula.

Reduction of the sulfoxide III with phosphorous tribromide resulted in the formation of the crystalline bromomethyl derivative IV in good yield.

According to our experience, compound III and IV are suitable materials for the synthesis of C-3′ substituted cephalosporin derivatives. The highly reactive allylic bromine atom of III and of IV could be readily reacted with nucleophiles, i.e. 1-methyl-1H-5-mercaptotetrazole to obtain V and VI respectively in excellent yield. No significant difference between the reactivity of III and IV was observed nor could $\Delta^3 \rightarrow \Delta^2$ isomerisation under the above conditions. Treatment of V with phosphorous tribromide under the same conditions described for III gave VI, but in significantly lower yield.

Reports in the literature have shown that either the removal or the partial halogenation of the trichloroethyl ester and the trichloroacetamido group of VI can be performed in one step.[14,15] Both the resulting chloroacetamido deriva-

tive and its deacylated[14-16] analoque might be further derivatized thus providing valuable intermediates or drugs in the cephalosporin series. Investigation of such transformation reactions are being in progress.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. ^{1}H-NMR spectra were recorded with a JEOL MH 100 (100 MHz) instrument in DMSO-d_6 solutions using TMS as an internal reference. Mass spectra were obtained with an AEI MS-902 high resolution spectrometer (70 eV). Thin layer chromatography was accomplished on DC-Alurolle Kieselgel 60F 254 (Merck), using 1:1 benzene-ethyl acetate mixture.

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-methyl-3-cephem-4-carboxylate 1-oxide (II).- A solution of 2.46 g (0.005 M) of 2',2',2'-trichloroethyl-7-trichloroacetamido-3-methyl-3-cephem-4-carboxylate (I) in chloroform (75 ml) was cooled to 0° and m-chloroperbenzoic acid (0.85 g) in chloroform (25 ml) was dropwise added with stirring. The reaction mixture was then stirred at room temperature for 3 hrs, the resulting precipitate was filtered and washed with ether to yield 2.1 g (81.8 %) of II, mp. 218-220° (from dioxane), tlc: R_f 0.60.

Anal. Calcd for $C_{12}H_{10}Cl_6N_2O_5S$: S, 6.32; N, 5.52; Cl, 41.95.

Found : S, 6.59; N, 5.39; Cl, 41.90.

^{1}H-NMR: δ 2.15 (s, 3H, $-CH_3$), 3.86, 3.93 (AB, 2H, J=18 Hz, S-CH_2), 5.13 (d, 1H, $J_{6,7}$=4.6 Hz, H-6), 5.98 (dd, 1H, H-7), 8.48 (d, 1H, $J_{NH,7}$=9 Hz, -NH), 5.04, 5.12 (AB, 2H, J=13 Hz, $-OCH_2CCl_3$).

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-bromomethyl-3-cephem-4-carboxylate 1-oxide (III). - Two g. of II was dissolved in 150 ml of acetic acid by heating. The solution was

cooled to room temperature and treated with N-bromosuccinimide (0.8 g) with exposure to a 400 W UV lamp and stirred for 80 minutes. The resulting precipitate was filtered and washed with ether to yield 1.4 g (60.8 %) of III, mp. 225° (from acetone), tlc: R_f 0.78.

Anal. Calcd for $C_{12}H_9BrCl_6N_2O_5S$: S, 5.47; N, 4.78.

Found : S, 5.47; N, 4.66.

^{1}H-NMR: δ 4.0, 4.08 (AB, 2H, J=18 Hz, S-CH_2), 4.59 (s, 2H, -CH_2Br), 5.24 (d, 1H, H-6), 6.07 (dd, 1H, $J_{6,7}$=5 Hz, H-7), 8.62 (d, 1H, $J_{NH,7}$=9.0 Hz, -NH), 5.08, 5.19 (AB, 2H, J=12 Hz, -OCH_2CCl_3).

Mass spectrum: 582 (M^+, 3.9 %); 503 (M-Br, 22 %); 475 (503-CO 100 %); 427 (475-SO, 14 %); 275 (M-307, 94 %); 234 (M-348, 33 %); 186 (M-396, 29 %); 131 (CH_2CCl_3, 86 %); 117 (CCl_3, 97 %).

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-bromomethyl-3-cephem-4-carboxylate (IV). - Compound III (1 g) was dissolved in dichloromethane (200 ml) containing phosphorous tribromide (1.5 ml). The solution was kept at room temperature for 3 hrs, extracted with 5% sodium hydrogen carbonate solution and water, dried over $MgSO_4$ and evaporated to dryness. The residue was crystallized from ether to give 0.7 g (71.4 %) of IV, mp. 165°, tlc: R_f 0.87.

Anal. Calcd for $C_{12}H_9BrCl_6N_2O_4S$: S, 5.62; N, 4.91.

Found : S, 5.48; N, 4.58.

^{1}H-NMR: δ 3.58, 3.84 (AB, 2H, J=18 Hz, -S-CH_2), 4.41, 4.54 (AB, 2H, J=12 Hz, -CH_2Br), 4.83, 5.06 (AB, 2H, J=12 Hz, -OCH_2CCl_3), 5.18 (d, 1H, $J_{6,7}$=5 Hz, H-6), 5.78 (dd, 1H, $J_{NH,7}$=8.0 Hz, H-7), 7.60 (d, 1H, -NH).

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-(1-methyl-1H-tetrazol-5-yl)-thio-methyl-3-cephem-4-carboxylate 1-oxide (V).

- To a solution of 1-methyl-1H-5-mercapto-tetrazole (0.116 g, 0.001 M) and triethylamine (0.14 ml) in acetone (20 ml) a solution of III (0.58 g) in acetone (20 ml) were added. After storing at room temperature for 30 min. the reaction mixture was diluted with water and the crystalline product V was isolated by filtration, 0.5 g (80.5 %); mp. 178° (from methanol), tlc: R_f 0.28.

Anal. Calcd for $C_{14}H_{12}Cl_6N_6O_5S_2$: S, 10.32; N, 13.53; Cl, 34.24

Found : S, 10.42; N, 13.46; Cl, 33.67.

^{1}H-NMR: δ 4.28 (s, 3H, N-CH_3), 4.26, 4.46(AB, 2H, S-CH_2-), 4.64, 5.14 (AB, 2H, -CH_2S), 5.40, 5.60 (AB, 2H, CH_2CCl_3), 5.48 (d, 1H, H-6), 6.44 (dd, 1H, H-7), 9.02 (d, 1H, NH).

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-(1-methyl-1H-tetrazol-5-yl)thio-methyl-3-cephem-4-carboxylate (VI)

a. Preparation of VI from V was performed as described above for the preparation of IV. The yield of VI was 55 %.

b. Preparation of VI from IV and 1-methyl-1H-5-mercapto-tetrazole was carried as described above for the synthesis of V.

After removal of triethylamine hydrobromide by filtration the solution was evaporated to dryness. The residue was dissolved in ethyl acetate and extracted with water. The organic layer was dried over $MgSO_4$ and evaporated to dryness and the residue was treated with ether to yield amorphous VI (75 %), tlc: R_f 0.80.

Anal. Calcd for $C_{14}H_{12}Cl_6N_6O_4S_2$: S, 10.59; N, 13.88; Cl, 35.15

Found : S, 10.45; N, 13.64; Cl, 34.90.

^{1}H-NMR: δ 4.28 (s, 3H, $-NCH_3$), 4.20 (s, 2H, $S-CH_2$), 4.71, 4.97 (AB, 2H, $-CH_2S$), 5.40, 5.57 (AB, 2H, CH_2CCl_3), 5.66 (d, 1H, H-6), 6.04 (dd, 1H, J=5 and 7 Hz, H-7), 10.53 (d, 1H, J=7 Hz, NH).

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