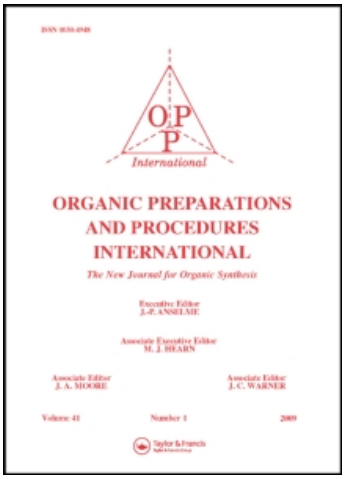

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TRANSFORMATION OF A 3-BROMOMETHYL-CEPHEM INTO 3-ACETOXYMETHYL-CEPHEM DERIVATIVES

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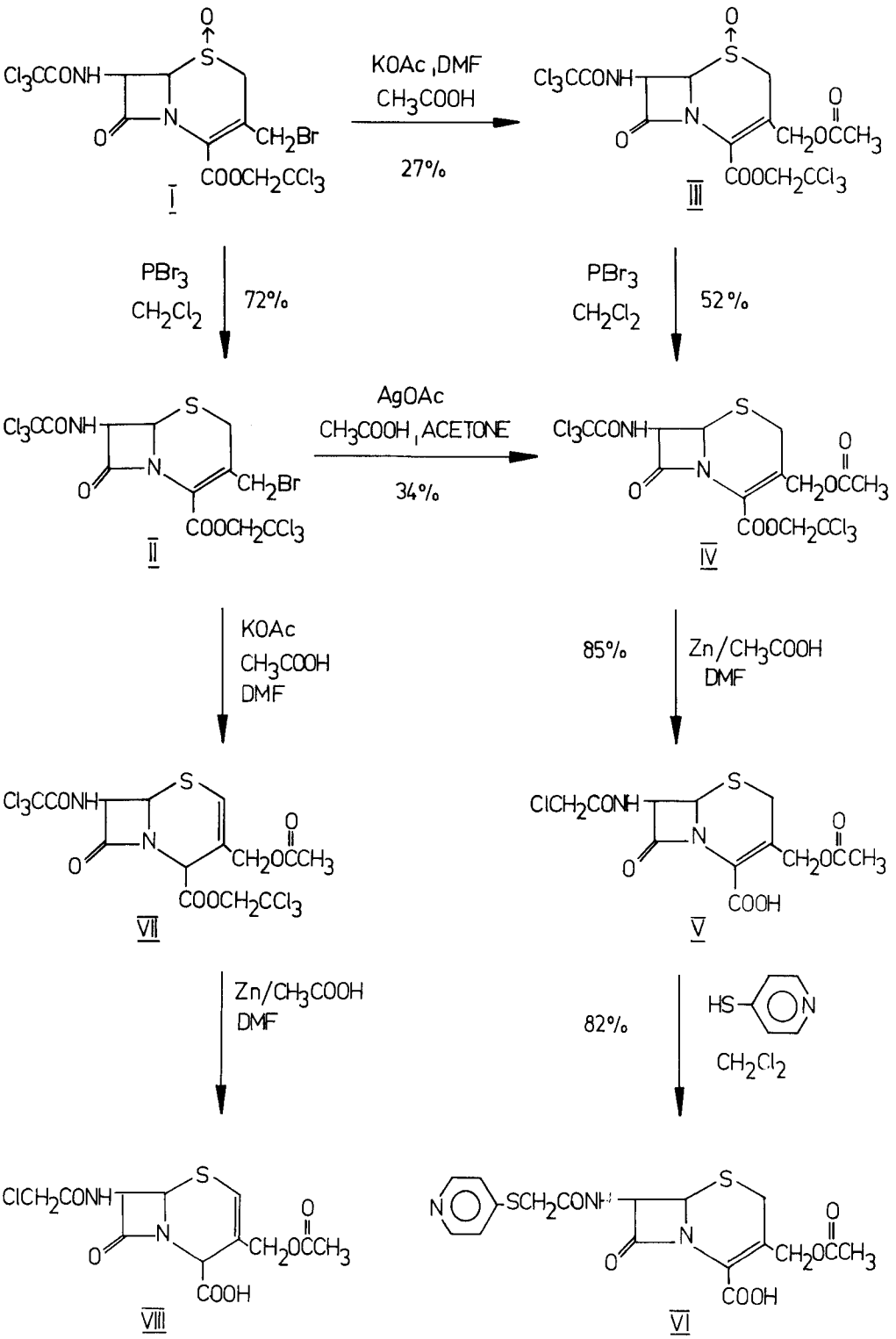
Recent results have shown[1] that both 2',2',2'-trichloroethyl-7-trichloroacetamido-3-bromomethyl-3-cephem-4-carboxylate (II) and the corresponding 1-oxide (I) are valuable intermediates for further chemical transformations and this communication describe the replacement of the bromine atom of I and II by acetoxy function, the removal of the protecting groups, and also, the conversion of V into Cephapirin[2] (VI). Nucleophilic substitution of the bromine atom of I was performed with potassium acetate in N,N-dimethylformamide in the presence of acetic acid at ambient temperature and the crystalline acetoxymethyl derivative III was isolated in 27 % yield. The structure of III was substantiated by elemental analysis, ^{1}H-NMR spectroscopic investigation and by comparison of its physical data (mp., tlc) with that of the reference compound prepared from 7-aminocephalosporanic acid. The most significant change found in the ^{1}H-NMR spectrum of III, as compared to that of I, is the appearance of the methyl signal of the acetoxy group at δ 2.0. Reduction of the acetoxy



compound III with phosphorous tribromide in dichloromethane gave 52 % of crystalline de-oxygenated IV. The C-2 methylene signals at δ 3.36 and 3.68, characteristic for Δ^3-cephalosporins, and the methyl signal of the acetoxy group (δ 2.16) in the ^{1}H-NMR spectrum clearly proved the structure of IV. In addition, the physical data of IV was found to be identical with that of the authentic sample synthesized from 7-aminocephalosporanic acid.

On the other hand, the reaction of the bromomethyl derivative II with potassium acetate under the conditions given for the conversion I → III afforded exclusively the Δ^2-3-acetoxymethyl analogue VII (43 %). Instead of the C-2 methylene proton signals, present in the ^{1}H-NMR spectrum of IV, the appearance of C-2 and C-4 proton resonances (δ 6.94 and 5.36 respectively) was detected in the spectrum of VII, unequivocally indicating that a $\Delta^3 \rightarrow \Delta^2$ isomerization had taken place during the reaction. The resonance of the methylene protons of the acetoxy group (δ 2.16) was unchanged.

The replacement of the bromo atom of II by acetoxy without the isomerization of the double bond could be performed in 33 % yield by treatment with silver acetate and acetic acid[3]. In contrast to the well-known method of Webber et al.[4], the advantage of the application of I and II for the synthesis of 3-acetoxymethyl-Δ^3-cephem derivatives is that no alkaline isomerization is required. Consequently the hydrolysis of the carboxylate function does not take place, obviating the need for repeated protection of the carboxyl group. The lowest yields were obtained during the exchange of bromine for the acetoxy

function.

Treatment of VII and IV with zinc and acetic acid[5,6] in N,N-dimethlyformamide gave the crystalline 7-chloroacetamido-cephalosporanic acids VIII (Δ^2) and V (Δ^3), respectively, in good yield. The reaction steps II → VII → VIII performed as a one-pot operation without the isolation of VII gave the product VIII in an overall yield of 57 %.

According to the results of Cocker et al.[7], the chloro-acetamido side-chain of V can be conveniently removed by treat-ment with thiourea. Compound V can also be directly used for the production of several semi-synthetic cephalosporins by the substitution of the chlorine atom with nucleophiles. For example, treatment of V with 4-mercaptopyridine in dichloro-methane, in the presence of triethylamine, afforded Cephapirin (VI), of a compound pharmaceutical importance, in excellent yield (82 %). Further modifications of deacetoxycephems at positions C-3' and C-7 are presently under investigation.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. ^{1}H-NMR spectra were recorded with a JEOL MH-100 (100 MHz) intrument using TMS as internal reference. Thin layer chromatography was accomplished on DC-Alurolle Kieselgel 60F254 (Merck) using 1:1 benzene-ethyl acetate (system A), 7:3 benzene-ethyl acetate (system B) or 95:5 acetone-acetic acid (system C) mixtures.

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-acetoxymethyl-3-cephem-4-karboxylate 1-oxide (III).- A mixture of the bromomethyl derivative I (0.001 M), N,N-dimethylformamide

(20 ml), acetic acid (1 ml) and potassium acetate (0.005 M) was stirred at room temperature for 2 hours. The reaction mixture was then diluted with water to ca. 60 ml and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was purified by preparative layer chromatography (on Kieselgel $60F_{254}$, system B) to obtain 150 mg (27 %), mp. 182° (from ethanol), tlc: R_f (A) 0.46.

Anal. Calcd for $C_{14}H_{12}Cl_6N_2O_7S$: S, 5.67; N, 4.95; Cl, 37.64.
Found : S, 5.70; N, 4.91; Cl, 37.22.

^{1}H-NMR (DMSO-d_6,ppm): δ 2.00 (s, 3H, $-CH_3$), 3.80, 4.20 (AB, 2H, $S-CH_2$), 4.70-5.16 (m, 5H, H-6, $2CH_2$), 6.12 (dd, 1H, H-7), 8.72 (d, 1H, NH).

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-acetoxymethyl--2-cephem-4-carboxylate (VII).- Reaction of the bromomethyl derivative II (0.001 M) was performed as described above for the preparation of III. The pale yellow syrupy product was directly used for the synthesis of VIII. 237 mg (43.3 %), tlc: R_f (A) 0.83. ^{1}H-NMR (DMSO-d_6, ppm): δ 2.16 (s, 3H, CH_3), 4.80 (s, 2H, CH_2), 5.10 (s, 2H, CH_2), 5.36 (s, 1H, H-4), 5.40 (d, 1H, H-6), 5.62 (dd, 1H, H-7), 6.94 (s, 1H, H-2), 10.24 (d, 1H, NH).

2',2',2'-Trichloroethyl-7-trichloroacetamido-3-acetoxymethyl-3-cephem-4-carboxylate (IV).- a. A mixture of II (0.001 M), silver acetate (0.0012 M), acetone (5 ml) and acetic acid (2 ml) was stirred at room temperature for two hours. The product IV was isolated by preparative layer chromatography

(on Kieselgel $60F_{254}$, system B) to obtain 185 mg (33.7 %), mp. 130° (from ether), tlc: R_f (A) 0.83.

Anal. Calcd for $C_{14}H_{12}Cl_6N_2O_6S$: N, 5.10; Cl, 38.74.

Found : N, 4.96; Cl, 38.26.

^{1}H-NMR ($CDCl_3$, ppm): δ 2.16 (s, 3H, CH_3), 3.36, 3.68 (AB, 2H, SCH_2), 4.64-5.20 (m, 5H, H-6, $2CH_2$), 5.72 (dd, 1H, H-7), 8.16 (d, 1H, NH).

b. Compound IV was obtained in 52% yield by the reduction of the 1-oxide III as described earlier[1].

7-Chloroacetamido-3-acetoxymethyl-3-cephem-4-carboxylic acid (V).- To a solution of IV (0.001 M) in N,N-dimethylformamide zinc dust (0.58 g) and acetic acid (0.75 g) were added and the mixture was stirred first at 0° for 30 min. and then at room temperature for 1 1/2 hrs. After filtration of unreacted zinc dust the filtrate was diluted with water to cca. 60 ml the pH of the solution was adjusted to 1 with diluted hydrochloric acid and then extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$ and concentrated. The residue was washed with ether to obtain 295 mg (84.7 %) of V, mp. 168° (from acetone-petroleum ether), tlc: R_f(C) 0.70.

Anal. Calcd for $C_{12}H_{13}ClN_2O_6$: N, 8.03; Cl, 10.16.

Found: N, 7.76; Cl, 10.15.

^{1}H-NMR (DMSO-d_6, ppm): δ 2.20 (s, 3H, CH_3), 3.64, 3.82 (AB, 2H, SCH_2), 4.32 (s, 2H, $ClCH_2$), 4.88, 5.20 (AB, 2H, CH_2-), 5.32 (d, 1H, H-6), 5.88 (dd, 1H, H-7), 9.36 (d, 1H, NH).

7-Chloroacetamido-3-acetoxymethyl-2-cephem-4-carboxylic acid (VIII).- Transformation of II into VIII was carried out in

one-pot operation involving the procedures described for the preparation of VII and V to yield 197 mg (overall yield 56.6%), mp. 174° (from ether), tlc: R_f(C) 0.67.

Anal. Calcd for $C_{12}H_{13}ClN_2O_6$: S, 9.19; N, 8.03; Cl, 10.16

Found : S, 9.15; N, 8.03; Cl, 10.16.

^{1}H-NMR (DMSO-d_6, ppm): δ 2.16 (s, 3H, CH_3), 4.28 (s, 2H, CH_2Cl), 4.80 (s, 2H, CH_2), 5.04 (s, 1H, H-4), 5.32 (d, 1H, H-6), 5.56 (dd, 1H, H-7), 6.84 (s, 1H, H-2), 9.42 (d, 1H, NH).

Cephapirin (VI).- A suspension of V (0.001 M), 4-mercapto-pyridine (0.001 M) and triethylamine (0.001 M) in dichloro-methane (7 ml) was stirred for 4 hrs at room temperature. It was then filtered, the crystals were washed with dichloromethane to obtain 348 mg (82.2 %), mp. 155° (acetone-water), lit.[2] mp. 155°.

Anal. Calcd for $C_{17}H_{17}N_3O_6S_2$: S, 15.14; N, 9.92.

Found : S, 15.14; N, 9.95.

^{1}H-NMR (DMSO-d_6, D_2O, ppm): δ 2.22 (s, 3H, CH_3), 3.60, 3.88 (AB, 2H, SCH_2), 4.16 (s, 2H, CH_2), 4.92, 5.20 (AB, 2H, CH_2), 5.26 (d, 1H, H-6), 5.86 (d, 1H, H-7), 7.68 (d, 2H, py), 8.62 (d, 2H, py).

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REFERENCES

1. I. Miskolczi, F. Sztaricskai and R. Bognár, Org. Prep. Proced. Int., 13, 315 (1981).

2. L. B. Crast, R. G. Graham and L. C. Cheney, J. Med. Chem. 16, 1413 (1973).

3. G. A. Koppel, M. D. Kinnick and L. J. Nummy, J. Am. Chem. Soc., 99, 2822 (1977).

4. J. A. Webber, E. M. Van Heyningen and R. T. Vasileff, ibid., 91, 5674 (1969).

5. Ger. Patent 24.42.661; Chem. Abst., 83, 43355a (1975).

6. Ger. Patent 24.42.663; Chem. Abst., 83, 43356a (1975).

7. J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C.P. Sly and G. A. Sommerfield, J. Chem. Soc., 5015 (1965).

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