ORALLY ACTIVE CEPHALOGLYCIN ESTERS

E. Binderup, W. O. Godtfredsen and K. Roholt
Leo Pharmaceutical Products, 2750 Ballerup, Denmark

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The preparation of the acetoxymethyl and pivaloyloxymethyl esters of cephaloglycin is described. These esters are well absorbed from the gastro-intestinal tract and after the absorption are cleaved enzymatically with the liberation of cephaloglycin. As a result high blood- and tissue-levels of the latter are attained.

In spite of their inherent stability towards acids, semisynthetic cephalosporins are generally not absorbed from the gastro-intestinal tract\(^1\), and it has long been an objective for research in this field to provide orally active derivatives.

A step towards this goal has been achieved by the preparation of cephaloglycin (7-\((\alpha\text{-}\text{aminophenylacetamido})\text{-}\text{cephalosporanic acid}) (1a) which has an excellent antimicrobial spectrum and is absorbed to some extent when given by the oral route\(^2,9\). However, its absorption is incomplete\(^6,4\) and because of the modest blood levels obtained it is mainly used in the treatment of urinary tract infections\(^6\).

Cephalexin (1b), the deacetoxy analogue of cephaloglycin, was subsequently found to be absorbed much more efficiently, and blood- and tissue-levels obtained after oral administration of this compound are considerably higher than those obtained after administration of a corresponding dose of cephaloglycin\(^4,5\). However, the \textit{in vitro} activity of cephalexin against most bacteria is considerably lower than that of cephaloglycin. Thus, its increase in potential effectiveness associated with improvement in absorption is opposed by its relatively lower activity.

\[
\begin{align*}
\text{a. } & \text{OAc} & \text{b. } & \text{H} & \text{c. } & \text{OAc} \text{CH}_3\text{COCH}_3 & \text{d. } & \text{OAc} \text{CH}_3\text{COOC}(\text{CH}_3)_2 \\
\end{align*}
\]

In previous papers from this laboratory\(^6,7\) it has been shown that the oral absorption of ampicillin (2a) can be substantially improved by converting it into an acyloxymethyl ester, for example the pivaloyloxymethyl ester called pivampicillin (2b). The hydrochloride of pivampicillin is absorbed rapidly and almost quantitatively from the gastro-intestinal tract and after absorption is hydrolyzed with the liberation of ampicillin. As a result of this superior absorption, the blood levels and urinary excretion
of ampicillin obtained after oral administration of pivampicillin are as high as those obtained after intramuscular injection of an equivalent amount of ampicillin\(^8,9\)).

The structural similarity between ampicillin (2a) and cephaloglycin (1a) and the utility of pivampicillin (2b) encouraged us to examine the possibility of improving the oral absorption of cephaloglycin by the synthesis of its acyloxymethyl esters. We now report the synthesis of the acetyloxymethyl ester (1c) and the pivaloyloxymethyl ester (1d), and the results of comparative absorption studies between these two esters and cephaloglycin.

**Chemistry**

The sodium salt of the commercially available cephalosporin, cephalothin (3), was converted into a mixture of the acetyloxymethyl esters 4 and 5\(^10\)) on reaction with chloromethyl acetate. In order to obtain pure 5, the mixture of the \(\Delta^2\) and \(\Delta^3\) isomers was oxidized with \(m\)-chloroperbenzoic acid to the sulfoxide 6, which subsequently was reduced to 5 with phosphorus trichloride according to the procedure of Kaiser et al.\(^11\))

Conversion of 5 into the 7-aminocephalosporanic ester 7 was accomplished by a method analogous to that described for the preparation of 7-aminocephalosporanic acid (7-ACA)\(^12\)) and 6-aminopenicillanic acid (6-APA)\(^13\)). Treatment of 5 with PCl\(_3\) in CHCl\(_3\) followed by reaction with \(n\)-propanol and hydrolysis yielded 7 which was isolated as its crystalline hydrochloride. Acylation of 7 with \(d-\alpha\)-azidophenylacetyl chloride smoothly gave 8 which on catalytic hydrogenation was converted into 1c-isolated as its amorphous hydrochloride.

The pivaloyloxymethyl ester (1d) was prepared from potassium 7-(\(d-\alpha\)-azidophenylacetamido)-cephalosporanate (9) which on reaction with chloromethyl pivalate afforded
a mixture of the $\Delta^2$ and $\Delta^3$ isomers 10 and 11. Oxidation to the sulfoxide 12 followed by reduction with sodium dithionite and acetylchloride\(^{14}\) afforded pure 11. The azido-ester (11) by catalytic hydrogenation yielded 1d as its hydrochloride.

**Biological Properties**

**Hydrolysis In Vitro**

We have shown that the cephaloglycin esters 1c and 1d are hydrolyzed with the liberation of cephaloglycin in the presence of human serum.

The rate of hydrolysis was studied at pH 7.45 and 37°C in the presence of 10% human serum. The method is based on the fact that intact ester can be removed from the reaction mixture by extraction with ethyl acetate whereas cephaloglycin remains in the aqueous phase. At intervals aliquots were extracted and both phases subjected to TLC.

By using this method the half-lives of 1c and 1d were shown to be less than 5 minutes and 10~20 minutes, respectively.

**Absorption and Distribution in Rats**

Blood- and tissue concentrations of cephaloglycin after oral administration of equimolar amounts of cephaloglycin, 1c HCl and 1d HCl are shown in Table 1. The fact that the blood and tissue levels obtained after administration of the esters generally are higher than those obtained after administration of cephaloglycin indicates that the esters—in particular 1c—are better absorbed than the parent compound.

**Absorption and Excretion in Man**

In Table 2 and Fig. 1 are shown the serum levels of cephaloglycin attained after oral administration of cephaloglycin, 1c HCl and 1d HCl, respectively, to healthy volunteers in a cross-over

<table>
<thead>
<tr>
<th>Organ</th>
<th>Hours after administration</th>
<th>Concentration in $\mu g/ml$ or $\mu g/g$ of wet weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A B C</td>
</tr>
<tr>
<td>Blood</td>
<td>1</td>
<td>1.2 6.8 3.1</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
<td>1.3 3.7 3.3</td>
</tr>
<tr>
<td>Kidney</td>
<td>2</td>
<td>5.9 9.1 5.2</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>0.87 1.4 1.2</td>
</tr>
<tr>
<td>Spleen</td>
<td>2</td>
<td>0.37 0.57 0.46</td>
</tr>
</tbody>
</table>

Table 1. Mean concentrations of cephaloglycin in blood and tissues following oral administration of 100 mg/kg of cephaloglycin (A) and equimolar amounts of 1c HCl (B) and 1d HCl (C) to groups of 5 rats.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Serum concentrations ($\mu g/ml$)</th>
<th>Urinary excretion (0~6 hrs.) %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/2 1 2 4 6</td>
<td>A B C A B C A B C A B C A B C</td>
</tr>
<tr>
<td>DR</td>
<td>0.64 8.0 6.70 75 4.8 3.40 73 2.11 12 0.36 0.48 0.26 &lt;0.13 &lt;0.13 &lt;0.13 &lt;0.13</td>
<td>17 71 55</td>
</tr>
<tr>
<td>RS</td>
<td>0.6411 6.11 13 4.8 3.60 86 2.01 12 0.28 0.52 0.31 &lt;0.13 &lt;0.13 &lt;0.13 &lt;0.13</td>
<td>14 70 48</td>
</tr>
<tr>
<td>BN</td>
<td>0.30 6.5 5.60 56 3.4 4.00 50 1.11 12 &lt;0.13 0.19 0.13 &lt;0.13 &lt;0.13 &lt;0.13</td>
<td>13 58 74</td>
</tr>
<tr>
<td>JM</td>
<td>0.93 5.1 4.81 2.3 2.70 93 1.30 68 0.22 0.25 &lt;0.13 &lt;0.13 &lt;0.13 &lt;0.13 &lt;0.13</td>
<td>26 71 66</td>
</tr>
<tr>
<td>Mean</td>
<td>0.63 7.7 5.80 95 4.1 3.70 76 1.61 11 0.25 0.35 0.21 &lt;0.13 &lt;0.13 &lt;0.13 &lt;0.13</td>
<td>18 68 61</td>
</tr>
</tbody>
</table>

Table 2. Serum concentrations and urinary excretion of cephaloglycin following oral administration of 200 mg of cephaloglycin (A) and equimolar amounts of 1c HCl (B) and 1d HCl (C) to fasting, healthy volunteers.
study. The higher and earlier peak serum levels and the overall greater area under the serum level-time curves attained after administration of the esters clearly show that these compounds are more efficiently absorbed from the gastro-intestinal tract than cephaloglycin.

It is worth mentioning that the peak serum levels of cephaloglycin obtained after oral administration of 1c HCl and 1d HCl in amounts corresponding to 200 mg of cephaloglycin are significantly higher than those reported after intramuscular injection of 250 mg of cephaloglycin. The superior oral absorption of the esters is also reflected in the urinary recovery. Thus, the amount of cephaloglycin excreted in the urine during six hours after administration averages 68 and 61% of theory in the case of the esters 1c HCl and 1d HCl, respectively, whereas the corresponding average figure for cephaloglycin is only 18%.

The excellent activity of cephaloglycin against many pathogenic bacteria in association with the high and uniform blood levels of cephaloglycin obtained after oral administration of 1c and 1d make a clinical evaluation of these esters desirable.

**Experimental**

All melting points are corrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. The IR spectra were obtained with a Perkin-Elmer 21 spectrophotometer with an NaCl prism and the NMR spectra with a Varian Associates spectrometer, Model A-60A. Microanalyses were performed in the microanalytical laboratory of Leo Pharmaceutical Products by Mr. G. CORNAl and Mr. W. EGGER. Thin-layer chromatographic results were obtained on silica gel Merck HF254 (nach Stahl) and the chromatograms were visualized by using the chlorine-toluidine test15).

Acetoxymethyl 7-(2-thienylacetamido)-cephalosporanate sulfoxide (6)

To a suspension of 3 (27.9 g, 66.7 mmol) in dimethylformamide (250 ml) was added chloromethyl acetate (14.5 g, 133.4 mmol). The mixture was stirred at room temperature for 20 hours, diluted with ethyl acetate (1 liter) and washed successively with water, aqueous sodium bicarbonate and saturated sodium chloride. The organic phase was dried and evaporated in vacuo to leave an oil from which unreacted chloromethyl acetate was removed by extraction with petroleum ether. The remaining crude product (28 g)—shown by NMR spectroscopy to be a mixture of 4 and 5—was dissolved in chloroform (500 ml), cooled in ice, and stirred while 78% m-chloroperbenzoic acid (13.1 g, 59.2 mmol) in chloroform (200 ml) was added during 10 minutes. After 3 hours at room temperature the reaction mixture was washed with saturated sodium bicarbonate and saturated sodium chloride. The organic phase was dried and evaporated in vacuo. The residue crystallized from methanol to afford 21.1 g of 6, m.p. 186–187°C. An analytical sample was prepared by
Acetoxymethyl 7-(2-thienylacetamido)-cephalosporanate (5)

A solution of 6 (20.8 g, 42.9 mmol) in methylene chloride (1 liter) containing phosphorus trichloride (34.1 g, 234 mmol) was heated under reflux for 2 hours. After cooling to room temperature, the mixture was neutralized with saturated aqueous sodium bicarbonate, washed with water and dried. The resulting solution was treated with charcoal, filtered and evaporated in vacuo. The crude product crystallized from methylene chloride–diisopropyl ether to yield 10.5 g of 5, m. p. 137–139°C. Recrystallization from acetone–water afforded an analytical sample, m. p. 141–142°C. UV, λ<sub>max</sub> 238 mυ (ε 13000), 266 mυ (ε 8000). [α]<sub>D</sub> +39° (c 1, CHCl₃).

Anal. Calcd. for C₁₉H₂₀N₂O₈S₂: C 48.71, H 4.30, N 5.98, S 13.68

Found: C 48.61, H 4.32, N 5.91, S 13.64

Acetoxymethyl 7-amino-cephalosporanate hydrochloride (7, HC₁)

To a stirred solution of phosphorus pentachloride (6.37 g, 30.5 mmol) in dry, ethanol-free chloroform (110 ml) were added quinoline (7.2 ml, 61.0 mmol) and, after cooling to -10°C, 5 (10.5 g, 22.4 mmol). After stirring at -10°C for 20 minutes 1-propanol (33 ml, 0.44 mol) was added during 5 minutes. After a further 20 minutes at -10°C the mixture was poured into water (110 ml) and petroleum ether (500 ml) was added with stirring. The aqueous phase was separated and made alkaline with sodium bicarbonate. The oil which separated was taken up in ethyl acetate, and the solution was washed with water and saturated sodium chloride, dried and evaporated in vacuo. The residue was washed repeatedly by decantation with petroleum ether to remove quinoline. The remaining oil was dissolved in ethyl acetate and the hydrochloride crystallized by addition of 1 N hydrochloric acid in 2-propanol. The crystals were filtered off, washed with ether and dried to yield 4.8 g of 7 HCl. Recrystallization from methanol–ether afforded an analytical sample, m. p. >170°C (dec.). UV, λ<sub>max</sub> 268 mυ (ε 6900). [α]<sub>D</sub> +64° (c 1, 0.1 N HCl).

Anal. Calcd. for C₁₃H₁₆N₂O₇S·HCl: C 41.00, H 4.50, Cl 9.31, N 7.35

Found: C 41.00, H 4.58, Cl 9.35, N 7.40

Acetoxymethyl 7-(D-α-azidophenylacetamido)-cephalosporanate (8)

To a solution of 7, regenerated from its hydrochloride (3.3 g, 8.7 mmol), in ethyl acetate (30 ml) was added pyridine (0.81 ml, 10.0 mmol). The mixture was cooled in ice and stirred while D-α-azidophenylacetyl chloride (1.9 g, 9.7 mmol) in ethyl acetate (30 ml) was added during 10 minutes. After a further 20 minutes in the cold stirring was continued at room temperature for 1 hour. Then the mixture was was washed successively with aqueous sodium bicarbonate, 0.1 N hydrochloric acid and water, dried and evaporated in vacuo to leave 3.9 g of a yellow oil which crystallized from ethyl acetate–cyclohexane to yield 3.2 g of 8, m. p. 104–105°C. Recrystallization from methanol–water afforded an analytical sample, m. p. 105–106°C. UV, λ<sub>max</sub> 265 mυ (ε 7600). [α]<sub>D</sub> -45° (c 1, CHCl₃).


Found: C 49.93, H 4.29, N 14.04, S 6.52

Acetoxymethyl 7-(D-α-aminophenylacetamido)-cephalosporanate hydrochloride (1c HC₁)

A solution of 8 (3.8 g, 7.6 mmol) in a mixture of tetrahydrofuran (120 ml) and water (50 ml) was placed in a four-necked 250 ml-flask equipped with a stirrer, gas inlet and outlet tubes, a glass-calomel combination electrode and a buret controlled by an automatic titrator. The system was flushed with nitrogen and after adding 10% Pd-C (3 g) hydrogen was bubbled through the mixture with stirring, a pH value of 3 being maintained by addition of 1 N hydrochloric acid via the titrator. When the consumption of acid had ceased the system was flushed with nitrogen and the catalyst removed by filtration. Tetrahydrofuran was evaporated in vacuo and the aqueous phase was extracted with ethyl
acetate to remove any remaining starting material. The aqueous layer was separated and freeze-dried to afford 3.1 g of 1\(\text{c}\) HCl as a colourless, amorphous powder which showed only one spot on thin-layer chromatography in the following solvent systems: \(n\)-butanol – acetic acid – water (4 : 1 : 1), Rf 0.53 and \(n\)-butyl acetate – \(n\)-butanol – acetic acid – methanol – 1/15 M phosphate buffer (pH 5.8) (80 : 15 : 40 : 5 : 24), Rf 0.33. UV \(\lambda_{	ext{max}}^\text{ELOH} = 264\) m\(\mu\) (\(E_{1\%\text{cm}}\) 127). NMR (CD\(\text{3}\)OD, tetramethylsilane as internal standard) \(\delta\) 2.04 (3H, s), 2.09 (3H, s), 3.42 (1H, d, \(J=18\)Hz), 3.60 (1H, d, \(J=18\)Hz), 4.76 (1H, d, \(J=14\)Hz), 5.06 (1H, d, \(J=14\)Hz), 5.08 (1H, d, \(J=5\)Hz), 5.15 (1H, s), 5.85 (1H, m), 5.84 (1H, d, \(J=6\)Hz), 5.94 (1H, d, \(J=6\)Hz) and 7.54 (5H, s).

Anal. Calcd. for C\(\text{12}1\)H\(\text{24}1\)ClN\(\text{3}1\)O\(\text{8}1\)S\(\cdot\)H\(\text{2}1\)O: C 47.41, H 4.93, N 7.90, S 6.03

Found: C 47.32, H 5.14, N 7.73, S 5.74

Pivaloyloxymer 7-\(\text{d}\)-\(\alpha\)-azidophenylacetamido)-cephalosporanate sulfoxide (12)

Potassium 7-\(\text{d}\)-\(\alpha\)-azidophenylacetamido)-cephalosporanate\(\text{16}\) (3.0 g, 6.4 mmol) was suspended in dimethylformamide (25 ml) and chloromethyl pivalate (1.9 ml, 12.8 mmol) was added. After stirring at room temperature for 23 hours the mixture was diluted with ethyl acetate (100 ml) and washed successively with water, aqueous sodium bicarbonate and water. The organic solution was dried and evaporated in vacuo. The residue was washed repeatedly by decantation with petroleum ether to remove excess of chloromethyl pivalate. The resulting oil (2.7 g)—shown by NMR spectroscopy to be a mixture of \(10\) and \(11\)—was dissolved in chloroform (75 ml). The solution was cooled in ice and stirred while 78 % \(m\)-chloroperbenzoic acid (1.1 g) in chloroform (50 ml) was added during 10 minutes. After 3 hours at room temperature the mixture was washed with saturated sodium bicarbonate and saturated sodium chloride. The solution was dried and evaporated in vacuo to give 2.7 g of crude product which crystallized from methanol to yield 1.7 g of 12, m.p. 99–100°C. UV, \(\lambda_{	ext{max}}^\text{ELOH} = 270\) m\(\mu\) (\(E_{1\%\text{cm}}\) 8700), [\(\alpha\)]\(\text{D}1\) \(\text{P}1\) –16° (c 1, CHCl\(3\)).

Anal. Calcd. for C\(\text{24}1\)H\(\text{2}7\)N\(\text{5}1\)O\(\text{9}1\)S: C 51.33, H 4.84, N 12.47, S 5.71

Found: C 51.08, H 4.88, N 12.55, S 5.80

Pivaloyloxymer 7-\(\text{d}\)-\(\alpha\)-azidophenylacetamido)-cephalosporanate hydrochloride \(\text{1d}\) HCl

On catalytic hydrogenation under conditions identical with those described for the conversion of 8 into 1\(\text{c}\) HCl, \(11\) (4.0 g, 7.3 mmol) was transformed into 1\(\text{d}\) HCl (3.0 g) which was obtained as a colourless, amorphous powder. This product showed only one spot on thin-layer chromatography in the following solvent systems: \(n\)-butanol – acetic acid – water (4 : 1 : 1), Rf 0.62 and \(n\)-butyl acetate – \(n\)-butanol – acetic acid – methanol – 1/15 M phosphate buffer (pH 5.8) (80 : 15 : 40 : 5 : 24), Rf 0.42. UV \(\lambda_{	ext{max}}^\text{ELOH} = 263\) m\(\mu\) (\(E_{1\%\text{cm}}\) 111). NMR (CD\(\text{3}\)OD, tetramethylsilane as internal standard) \(\delta\) 1.23 (9H, s), 2.07 (3H, s), 3.42 (1H, d, \(J=18.5\)Hz), 3.59 (1H, d, \(J=18.5\)Hz), 4.84 (1H, d, \(J=14\)Hz), 5.11 (1H, d, \(J=14\)Hz), 5.01 (1H, d, \(J=5\)Hz), 5.13 (1H, s), 5.75 (1H, m), 5.89 (1H, d, \(J=5.5\)Hz), 5.93 (1H, d, \(J=5.5\)Hz), 7.18 (1H, d, \(J=9\)Hz) and 7.42 (5H, s).

Pivaloyloxymer 7-\(\text{d}\)-\(\alpha\)-aminophenylacetamido)-cephalosporanate hydrochloride \(\text{1d}\)

To a solution of 12 (4.2 g, 7.5 mmol) in dimethylformamide (50 ml) was added sodium dithionite (4.2 g, 24.1 mmol). The suspension was cooled in ice and stirred while acetyl chloride (24.5 ml, 34.4 mmol) was added during 10 minutes. The mixture was stirred at 3–5°C for a further 30 minutes, then poured into saturated sodium bicarbonate and extracted with ethyl acetate. The organic phase was washed with water, dried, treated with charcoal and evaporated in vacuo to afford 3.3 g of 11 as a yellow foam. IR \(\nu_{\text{max}}^\text{C\(\text{H}1\)}\) 2122, 1791, 1744 and 1694 cm\(^{-1}\). NMR (CDCl\(3\), tetramethylsilane as internal standard) \(\delta\) 1.23 (9H, s), 2.07 (3H, s), 3.42 (1H, d, \(J=18.5\)Hz), 3.59 (1H, d, \(J=18.5\)Hz), 4.84 (1H, d, \(J=14\)Hz), 5.11 (1H, d, \(J=14\)Hz), 5.01 (1H, d, \(J=5\)Hz), 5.13 (1H, s), 5.75 (1H, m), 5.89 (1H, d, \(J=5.5\)Hz), 5.93 (1H, d, \(J=5.5\)Hz), 7.18 (1H, d, \(J=9\)Hz) and 7.42 (5H, s).

Pivaloyloxymer 7-\(\text{d}\)-\(\alpha\)-aminophenylacetamido)-cephalosporanate hydrochloride \(\text{1d}\) HCl

On catalytic hydrogenation under conditions identical with those described for the conversion of 8 into 1\(\text{c}\) HCl, \(11\) (4.0 g, 7.3 mmol) was transformed into 1\(\text{d}\) HCl (3.0 g) which was obtained as a colourless, amorphous powder. This product showed only one spot on thin-layer chromatography in the following solvent systems: \(n\)-butanol – acetic acid – water (4 : 1 : 1), Rf 0.62 and \(n\)-butyl acetate – \(n\)-butanol – acetic acid – methanol – 1/15 M phosphate buffer (pH 5.8) (80 : 15 : 40 : 5 : 24), Rf 0.42. UV \(\lambda_{	ext{max}}^\text{ELOH} = 263\) m\(\mu\) (\(E_{1\%\text{cm}}\) 111). NMR (CD\(\text{3}\)OD, tetramethylsilane as internal standard) \(\delta\) 1.23 (9H, s), 2.07 (3H, s), 3.40 (1H, d, \(J=18\)Hz), 3.58 (1H, d, \(J=18\)Hz), 4.76 (1H, d, \(J=14\)Hz), 5.06 (1H, d, \(J=14\)Hz), 5.07 (1H, d, \(J=5\)Hz), 5.11 (1H, s), 5.83 (1H, m), 5.84 (1H, d, \(J=6\)Hz), 5.94 (1H, d, \(J=6\)Hz) and 7.53 (5H, s).

Anal. Calcd. for C\(\text{24}1\)H\(\text{3}0\)ClN\(\text{3}1\)O\(\text{8}1\)S\(\cdot\)H\(\text{2}1\)O: C 50.22, H 5.62, N 7.32, S 5.53

Found: C 50.05, H 5.47, N 7.16, S 5.53
Microbiological Assays

Concentrations of cephaloglycin in urine, serum and tissues were determined by the agar cup plate technique using Sarcina lutea ATCC 9341 as the test organism and cephaloglycin as the reference compound*.

Hydrolysis of 1c and 1d in vitro

The hydrolysis of 1c and 1d was studied at pH 7.45 and 37°C in the presence of 10 % human serum. The starting concentration of the esters was $2.47 \times 10^{-4} \text{M}$ corresponding to 100 $\mu$g/ml of cephaloglycin. Every five minutes 5 ml samples were extracted with 5 ml of ethyl acetate and both phases subjected to TLC (solvent system: n-butyl acetate–n-butanol–acetic acid–methanol–1/15 M phosphate buffer (pH 5.8) (80 : 15 : 40 : 5 : 24)). The amounts of cephaloglycin and intact esters were evaluated by comparison with known amounts of the appropriate reference compounds. In the case of 1c the hydrolysis was virtually complete after 5 minutes. For 1d the half-life was estimated to be 10~20 minutes under these conditions.

References

16) German patent application no. 1904585 (28th August, 1969)

* The authors wish to thank Dr. M. Gorman, Eli Lilly and Co. for a generous gift of cephaloglycin reference standard.