CROATICA CHEMICA ACTA CCACAA 49 (4) 779—795 (1977)

YU ISSN 0011-1643
CCA-1051 547.71
Original Scientific Paper

Dephthaloylation of Phthalimido-Containing Cephalosporins and Penicillins[1]

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Received December 28, 1976

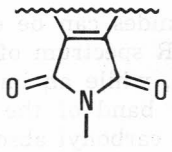
Dephthaloylation of phthalimido functionalized cephalosporins and penicillins via the corresponding phthalisoimides was performed. Experimental procedures and mechanism of reaction are described.

INTRODUCTION

It has been recognized that phthalimido-containing cephalosporins, penicillins, and monocyclic azetidinones are more stable to a wide variety of reaction conditions than the corresponding amido derivatives. Apparently the phthaloyl protection enhances the stability of the azetidinone ring system, and, therefore, many chemical reactions otherwise impracticable have been feasible with phthaloyl protected azetidinones. The obvious advantages of the phthaloyl protective group[2] have been overshadowed, however, by the lack of a selective method of removal of this function in the presence of a highly sensitive azetidinone ring system.

The well-known Ing-Manske method[3] for the removal of the phthaloyl group by hydrazinolysis of *N*-substituted phthalimides could not be applied to cephalosporins[4] and penicillins[5] having the phthalimido group. The reason that the phthaloyl group can not be successfully removed from cephalosporins and penicillins is that the azetidinone carbonyl function is, in fact, more reactive toward hydrazine than the phthalimido carbonyl. Therefore, undesirable azetidinone hydrazinolysis occurs preferentially. To circumvent this problem there was a need to enhance the reactivity of the imido functionality with respect to that of the azetidinone ring.

We believed that desired enhancement of the imido carbonyl reactivity could be achieved by conversion of the imide function **1** to that of an isoimide **2**. Moreover, we believed that in any given isoimido-azetidinone nucleophilic attack at the carbonyl group of isoimide would be the preferred process.



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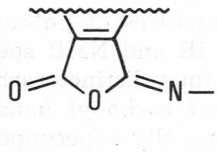

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If our hypothesis were correct, the desired dephthaloylation would occur without destroying the integrity of the bicyclic penicillin or cephalosporin ring system. To test this proposal several phthalimido protected cephalosporins and penicillins were selected for detailed study and converted to corresponding phthalisoimides.

Phthalimido protected compounds needed for our studies were prepared by several methods. Phthaloylation of 6-amino penicillanic acid (6-APA) and 7-amino deacetoxycephalosporanic acid (7-ADCA) with N-carbethoxy phthalimide was achieved according to the method described by Nefkens et al.[6] The obtained acids were esterified in accordance with the standard procedures described in the experimental section. Alternatively, 7-ADCA can be phthaloylated with o-phthaloyl dichloride in the presence of sodium bicarbonate in tetrahydrofuran at room temperature.[7] A similar treatment of the esters of 7-ADCA and 7-amino cephalosporanic acid (7-ACA) with o-phthaloyl dichloride afforded, however, the corresponding 7-phthalisoimide which was subsequently isomerized with hydroxylamine to the desired 7-phthalimido compound. Apparently in the case of 7-ADCA the intermediate isoimide was isomerized in the presence of the sodium carboxylate functionality.[8]

The first step in the proposed dephthaloylation is hydrolysis of the phthalimido compounds to their corresponding phthalamic acids. Although a hydrolysis of this type with sodium hydroxide has been described,[9] we have found that in the case of phthalimido protected azetidinones, higher yields and products of high purity are obtained when the hydrolysis is carried out with $Na_2S \cdot 9H_2O$.

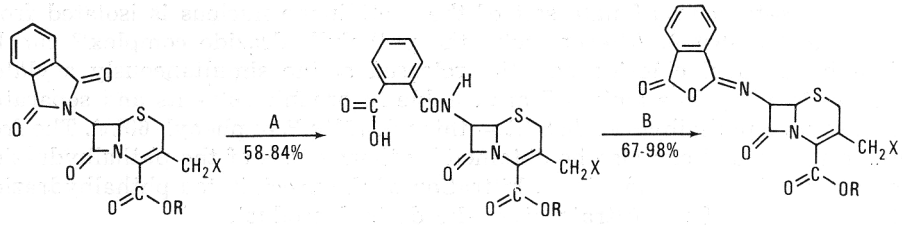
In both cephalosporins and penicillins the hydrolysis proceeds at 0—5 °C in aqueous acetone or tetrahydrofuran with reaction times of 5 to 15 minutes (longer times for cephalosporins) using 1 equiv of $Na_2S \cdot 9H_2O$ with the esters and 2 equiv of $Na_2S \cdot 9H_2O$ for the acids. This hydrolysis proceeds best with the acid derivatives in both penicillins and cephalosporins. Also, the greater the solubility of the ester in aqueous acetone or tetrahydrofuran, the higher the yields (68—90%), i. e. Me > *t*-Bu > *p*MB > *p*NB. During the hydrolysis of cephalosporin esters formation of 7-(2-carboxybenzamido)-3-methyl-2-cephem-4-carboxylic acid as a minor by-product was noted, but its high degree of insolubility allows for facile separation from the desired phthalamic acid.

Three routes to the phthalisoimides **5** from the corresponding phthalamic acids **4** have been used with equal success: (*a*) trifluoroacetic anhydride-triethylamine, (*b*) dicyclohexylcarbodiimide (DCC) and (*c*) ethyl chloroformate-triethylamine.[10] The reactions were performed in tetrahydrofuran at 0—5 °C for 10—30 min. All three methods were found equally applicable to the cephalosporins, but method c was found to be the preferable one for the penicillin phthalamic acids. The phthalisoimides **5** were obtained as stable compounds in good yield (67—97%) and were nearly always contaminated with small amounts of the corresponding phthalimido compounds **3**.

The structures of phthalisoimides and phthalimides can be easily distinguished by IR and NMR spectra. In general, the IR spectrum of an isoimide consists of four distinct carbonyl absorption bands, while an imide has only two apparent carbonyl bands; the high frequency band of the phthalimido group is generally superimposed on the azetidinone carbonyl absorption band, and the low frequency phthalimido carbonyl band is superimposed on the

SCHEME I

PHTHALISOIMIDES - PREPARATION



3 a-f 4 a-f 5 a-f

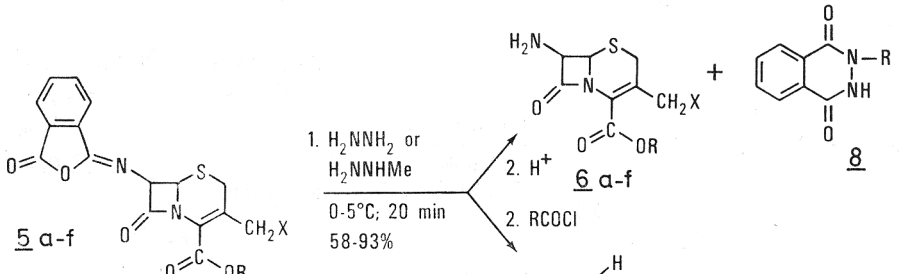
3 4 5	R	X
a	H	H
b	CH_3	H
c	t-Bu	H
d	p-$CH_3OC_6H_5$	H
e	t-Bu	AcO
f	p-$NO_2C_6H_5$	H

ester carbonyl absorption band.[11] In the NMR spectrum the aromatic protons of the phthalimido group appear like a broad singlet, while the phthalisoimide protons exhibit a broader more complex multiplet.

The final step in the dephthaloylation process involves hydrazinolysis of phthalisoimides. We have found that this reaction proceeds quickly and selectively. When an isoimide **5** is treated with 1 equiv of hydrazine in tetrahydrofuran at —20 °C for 20—30 min the phthaloyl group is removed and an amine

SCHEME II

PHTHALISOIMIDES - HYDRAZINOLYSIS



5 a-f 6 a-f 8

6 a R=H, X=H
b R=CH_3, X=H
c R=t-Bu, X=H
d R=p-$CH_3OC_6H_5$, X=H
e R=t-Bu, X=AcO
f R=p-$NO_2C_6H_5$, X=H

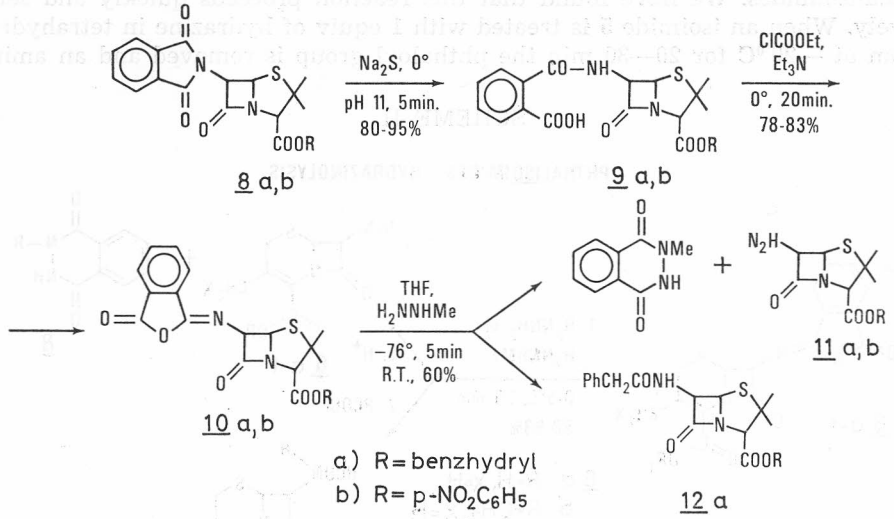
7 a R=t-Bu, X=OAc
b R=p-$NO_2C_6H_5$, X=H

salt of phthalylhydrazide is formed.[12] The desired amine can be separated from phthalhydrazide by mild digestion with *p*-toluenesulfonic acid or dilute hydrochloric acid. The highly insoluble phthalhydrazide is filtered, and the hydrochloride or *p*-toluenesulfonate salt of the azetidinone nucleus is isolated from the filtrate (55—95%). Alternatively, the phthalylhydrazide complex[12] can be broken by an acyl chloride and the released amine simultaneously acylated (90 °C, 8—15 min). The amides **7** are soluble in organic solvents and separated from insoluble phthalhydrazide **8** (R = thienyl, 75%; R = phenyl, 60%). The free amino ester or acid can also be obtained by thermolysis of the phthalhydrazide complex in refluxing chloroform. Filtration of the precipitated phthalhydrazide and evaporation of the filtrate gives the desired product.

A significant improvement in the yield and in the ease of isolation of the nucleus is realized when methylhydrazine is employed instead of hydrazine. This is attributed to the decreased acidity of the by-product *N*-methylphthalhydrazide **8** (with respect to phthalhydrazide). Because of such decreased acidity, no complex is formed with the free amine. Therefore, no heating or acid treatment of the reaction mixture is required. *N*-Methylphthalhydrazide separates from a chloroform solution (25 °C) of the methylhydrazine-phthalisoimide adduct leaving the free amine in solution. The advantages of using methylhydrazine are thus particularly noticeable when applied to the dephthaloylation of more sensitive substrates (e. g. penicillins).

SCHEME III

DEPHTHALOYLATION OF PENICILLINS



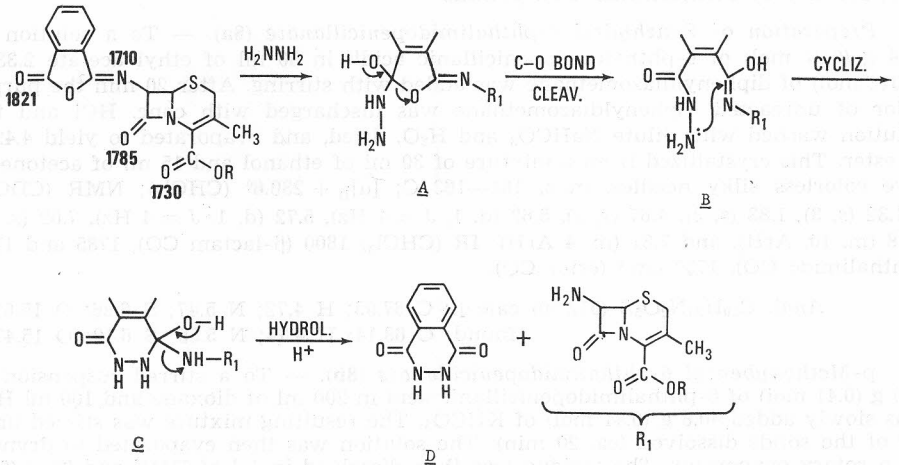
Hydrazinolysis of 6-phthalisoimidopenicillanates **8** to the corresponding esters of 6-APA has been accomplished only with *N*-methylhydrazine at —76 °C. Attempted hydrazinolysis of penicillin phthalisoimidides at 0 °C yields only decomposition products.

Mechanism

A survey of the literature revealed that isoimides undergo nucleophilic attack at carbonyl group as the favored process.[13] The carbonyl absorption (1821 to 1800 cm^{-1}) in the IR spectra of isoimides indicates also that carbonyl group is indeed the most reactive one in the molecule. Consequently, hydrazine preferentially attacks the isoimide carbonyl forming an addition intermediate **A**. Opening of the imino lactone **A** gives the corresponding hydrazide **B** which in turn cyclizes to a six-membered cyclic intermediate **C**. Finally, after the cleavage of the carbon-nitrogen bond, the desired amino nucleus and phthalhydrazide **D** are formed.

SCHEME IV

HYDRAZINOLYSIS OF PHTHALISOIMIDES - MECHANISM



If the mechanism involving the intermediacy of a hydrazide **B** is correct, it seemed that an alternative synthesis of this intermediate might also be practicable in the removal of the phthaloyl group. Moreover, the synthetic preparation of this intermediate could also prove the correctness of the proposed mechanism. We decided, therefore, to prepare this intermediate by reacting phthalamic acid with ethyl chloroformate in tetrahydrofuran at —10 °C for 15 min in the presence of triethylamine to form the mixed anhydride. This highly reactive anhydride was immediately treated with 1 equiv of anhydrous hydrazine at 0 °C for 5 min and converted to the expected hydrazide **B**, which in turn upon heating at 50—60 °C for 50 min was ring closed to the cyclic hydrazide **C**. This hydrazide was digested with acid for 5 min to provide the 6-aminocephalosporin and the by-product phthalhydrazide in good yield.

The formation of the isolated products clearly indicates that the amino group in **B** attacks the electrophilic carbonyl carbon resulting in the formation of cyclic hydrazide[14] (as depicted by **B** and **C**). The subsequent cleavage of the C-N bond in **C** results in formation of phthalhydrazide **D** and the expected amino nucleus.

The described dephthaloylation is relatively simple and fast. Although technically it has 3 chemical steps, the dephthaloylation can be performed easily in a short period of time. Moreover, no racemization has been observed during this high yielding dephthaloylation procedure. Recently this new method was successfully applied in the removal of the phthaloyl group from tricyclic azetidinones.[15] We hope that this study will result in the expanded applicability of the phthaloyl protective group in synthetic work.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Beckman IR-7 or Perkin-Elmer Model 21 or Infracord instruments. Tlc was done using silica gel plates. NMR spectra were taken on Varian Associates Model T-60, HR-60 or HA-100 spectrometers with TMS as internal standard.

Preparation of Phthalimido Compounds

Preparation of Benzhydryl 6-phthalimidopenicillanate (**8a**). — To a solution of 3.44 g (0.01 mol) of 6-phthalimidopenicillanic acid[16] in 30 ml of ethyl acetate 2.33 g (0.012 mol) of diphenyldiazomethane was added with stirring. After 20 min the purple color of unreacted diphenyldiazomethane was discharged with conc. HCl and the solution washed with dilute $NaHCO_3$ and H_2O, dried, and evaporated to yield 4.42 g of ester. This crystallized from a mixture of 30 ml of ethanol and 15 ml of acetone to give colorless silky needles, m. p. 161—163 °C; $[\alpha]_D$ + 230.6° ($CHCl_3$); NMR ($CDCl_3$) δ 1.32 (s, 3), 1.83 (s, 3), 4.67 (s, 1), 5.62 (d, 1, J = 4 Hz), 5.72 (d, 1, J = 4 Hz), 7.02 (s, 1), 7.38 (m, 10, ArH), and 7.81 (m, 4 ArH); IR ($CHCl_3$) 1800 (β-lactam CO), 1785 and 1735 (phthalimido CO), 1750 cm^{-1} (ester CO).

Anal. $C_{29}H_{24}N_2O_5S$ (512.50) calc'd.: C 67.95; H 4.72; N 5.47; S 6.26; O 15.61%
found: C 68.14; H 4.74; N 5.55; S 6.19; O 15.47%

p-*Methoxybenzyl 6-phthalimidopenicillanate* (**8b**). — To a stirred suspension of 135 g (0.41 mol) of 6-phthalimidopenicillanic acid in 200 ml of dioxane and 100 ml H_2O was slowly added 40.8 g (0.41 mol) of $KHCO_3$. The resulting mixture was stirred until all of the solids dissolved (ca. 20 min). The solution was then evaporated to dryness on a rotary evaporator. The residue was then dissolved in 1 l of DMF and 82 g (0.41 mol) of p-methoxybenzyl bromide[18] was added. The resulting mixture was stirred for 2 h and poured over 2 l of ice. The white precipitate was collected by filtration and thoroughly washed with H_2O. The crystals were then dried at room temperature in a vacuum over 24 h. Crude yield 157.7 g. The crude product was recrystallized from ethyl acetate and dried at room temperature; yield from recrystallization 122.3 g, m. p. 137—140 °C; NMR ($CDCl_3$) δ 1.42 (s, 3), 1.81 (s, 3), 3.82 (s, 3), 4.66 (s, 1), 5.18 (s, 2), 5.58 (d, 1, J = 4.5 Hz), 5.62 (d, 1, J = 4.5 Hz), and 6.8—8 Hz (m, 9, ArH).

Anal. $C_{24}H_{22}N_2O_6S$ (466.43) calc'd.: C 61.80; H 4.72; N 6.02; O 20.60; S 6.87%
found: C 62.06; H 4.69; N 6.22; O 20.71; S 6.72%

7-Phthalimido-3-methyl-3-cephem-4-carboxylic acid (**3a**)

A. *N-Carbethoxyphthalimide method.* — To a suspension of 181 g of 7-amino-3--methyl-3-cephem-4-carboxylic acid in 1700 ml of water, 142 g of $NaHCO_3$ was slowly added and then a solution of 186 g of *N*-carbethoxyphthalimide in 1 l of acetone was added dropwise in 30 min. After stirring for 3 h the solution was cooled in an ice water bath and acidified with 600 ml of 42.5% of H_3PO_4 to pH = 2.1. The precipitate was filtered, washed with water and vacuum dried giving 227 g of a mixture of the starting material and the desired phthalimido compound. The mixture was separated by extraction with warm acetone and ethyl acetate and 105 g of 7-ADCA was recovered. The yield of the phthalimido compound was 114 g. A sample (1 g) was crystallized from acetone (15 ml); colorless crystals, m. p. 223—225 °C; $[\alpha]_D$ + 428.02° (MeCN); IR (nujol) 1810, 1785, 1740, and 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 3.0 and 3.75 (ABq, 2, J = 14 Hz), 5.13 (d, 1, J = 4.5 Hz), 5.71 (d, 1, J = 4.5 Hz), and 7.82 (m, 4, ArH).

Anal. $C_{16}H_{12}N_2O_5S$ (344.27) calc'd.: C 55.81; H 3.51; N 8.14; O 23.23; S 9.31%
found: C 55.72; H 3.38; N 8.17; O 23.51; S 9.27%.

B. *Phthaloyl dichloride method*[7]. — To a suspension of 7-amino-3-methyl-3-cephem-4-carboxylic acid (424 mg, 2 mmol) and sodium bicarbonate (335 mg, 4 mmol) in 15 ml dry tetrahydrofuran at room temperature was added *o*-phthaloyl dichloride (0.3 ml, 2 mmol). After stirring for 1 h at room temperature, 2 ml of water was added and the mixture allowed to stir for an additional 45 min. The mixture was evaporated in vacuo to near dryness. The product was then shaken with 5% sodium bicarbonate solution (30 ml) and ethyl acetate (40 ml) until all material was in solution. The aqueous layer was separated, and after the pH was adjusted to 2.5 with 1 mol/dm^3 HCl, was washed with ethyl acetate (30 ml). The ethyl acetate layer was washed with brine (30 ml), dried ($MgSO_4$) and evaporated in vacuo to dryness. Recrystallization from acetone gave 7-phthalimido-3-methyl-3-cephem-4-carboxylic acid (280 mg, 39%) identical to the acid obtained via N-carbethoxyphthalimide method.

Methyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate (**3b**). — To a solution of 17.3 g (0.05 mol) of 7-phthalimido-3-methyl-3-cephem-4-carboxylic acid in 50 ml of acetone and 20 ml of water, 5 g (0.05 mol) of $KHCO_3$ was slowly added. The solution was then evaporated in vacuo to dryness. To the residue was added 38 ml of DMF and 5 ml of methyl iodide. The mixture was stirred for 3 h at room temperature after which time 100 g of ice was added. The solid product thereby formed was filtered and cristallized from 100 ml of 2-propanol and 100 ml of acetone. Yield: 7.91 g of crystals, m. p. 187—188 °C; IR ($CDCl_3$) 1790 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.31 (s, 3, CH_3), 3.0 and 3.75 (ABq, 2, J = 15 Hz), 3.85 (s, 3, CH_3), 5.15 (d, 1, J = 4.4 Hz), 5.74 (d, 1, J = 4.4 Hz) and 7.73 (m, 4, ArH).

Anal. $C_{17}H_{14}N_2O_5S$ (358.3) calc'd.: C 56.98; H 3.94; N 7.82; S 8.95%
found: C 56.75; H 3.66; N 7.53; S 8.89%.

t-*Butyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate* (**3c**). — A mixture of 13.76 g (40 mmol) of 7-phthalimido-3-methyl-3-cephem-4-carboxylic acid, 10 ml of conc H_2SO_4, 100 ml of dry dioxane and 50 ml of liquid isobutylene was stirred at room temperature in a sealed pressure bottle and then poured into an excess of ice cold aqueous $NaHCO_3$ (44 g)[17]. Extraction with ethyl acetate and evaporation in vacuo of the extract gave a crude ester which was crystallized from $CHCl_3$. The first crop gave 3.34 g of crystals, m. p. 189—191 °C and the second 1.72 g, m. p. 181—183 °C; $[\alpha]_D$ + + 77.7° (MeCN); IR ($CHCl_3$) 1800, 1785, and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9, *t*-Bu); 2.23 (s, 3, CH_3), 3.05 and 3.6 (ABq, 2, J = 16 Hz), 5.1 (d, 1, J = 4.5 Hz), 5.72 (d, 1, J = = 4.5 Hz) and 7.8 (m, 4, ArH).

Anal. $C_{20}H_{20}N_2O_5S$ (400.38) calc'd.: C 59.99; H 5.03; N 7.00; O 19.98; S 8.01%
found: C 60.27; H 4.91; N 7.04; O 20.06; S 7.74%.

p-*Methoxybenzyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate* (**3d**). — To a suspension of 13.4 g (38 mmol) of 7-phthalimido-3-methyl-3-cephem-4-carboxylic acid in 20 ml of dioxane and 10 ml of water was added slowly, 3.8 g of $KHCO_3$. The solution was evaporated to dryness and to the resulting potassium salt, 100 ml of DMF and 8.8 g of *p*-methoxybenzyl bromide[18] was added. After stirring for 2 h the mixture was poured onto 200 g of ice and extracted twice with ethyl acetate. The extract was washed with water and brine, dried, and the solvent was evaporated. The residue was recrystallized from ethyl acetate. Yield: 4.1 g of large crystals, m. p. 118—121 °C; the second crop 1.8 g; $[\alpha]_D$ + 41.2° (MeCN); IR ($CHCl_3$) 1800, 1785, 1745 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (s, 3, CH_3); 3.0 and 3.7 (ABq, 2, J = 15 Hz), 3.8 (s, 3, CH_3), 5.11 (d, 1, J = 4.5 Hz), 5.28 (s, 2, CH_3), 5.75 (d, 1, J = 4.5 Hz), 6.8—7.8 (m, 8).

Anal. $C_{24}H_{20}N_2O_6S$ (464.42) calc'd.: C 62.06; H 4.34; N 6.03; O 20.67; S 6.90%
found: C 62.15; H 4.31; N 6.32; O 20.88; S 6.82%.

t-*Butyl 7-phthalimido-3-acetoxymethyl-3-cephem-4-carboxylate* (**3e**)

A. *Cyclization of phthalamic acid method.* — A mixture of 3.28 g (10 mmol) of *t*-butyl 7-aminocephalosporanate,[17] 1.5 g (10 mmol) of phthalic anhydride and 25 ml of benzene was refluxed for 2 h by using a Dean-Stark collector. After cooling, the solution was washed with $NaHCO_3$ (1.68 g in 20 ml of H_2O), water, brine and dried.

The solvent was evaporated to give 1.22 g of a neutral product which was chromatographed over silica gel using a benzene/ethyl acetate gradient. Fraction 54—87 gave 330 mg of phthalimido compound which was recrystallized from dichloromethane/ether; prisms, m. p. 176—178 °C; $[\alpha]_D$ + 43.4° (MeCN); IR ($CHCl_3$) 1800, 1785 and 1735 cm^{-1}; λ_{EtOH} 260 mμ (ε = 10, 000); NMR ($CDCl_3$), δ 1.55 (s, 9, t-Bu); 2.1 (s, 3, CH_3), 3.5 (s, 2, CH_3); 4.9 and 5.3 (ABq, 2, J = 14 Hz); 5.1 (d, 1, J = 4.5 Hz); 5.82 (d, 1, J = 4.5 Hz), and 7.82 (m, 4, ArH).

Anal. $C_{22}H_{22}N_2O_7S$ (458.41) calc'd.: C 57.63; H 4.84; N 6.11; O 24.43; S 6.99%
found: C 57.56; H 4.60; N 6.31; O 24.60; S 6.90%.

After removal of the neutral product, the aqueous portion was acidified to pH = 3.6 and the acid extracted with ethyl acetate. Evaporation of the solvent provided 2.9 g of *t*-butyl 7-(2-carboxybenzamido) cephalosporanate. This material was dissolved in 50 ml of benzene, 15 mg of imidazole was added, and the resulting mixture was refluxed for 30 min (Dean-Stark). After work-up procedure and chromatography, 430 mg of *t*-butyl 7-phthalimido cephalosporanate was obtained.

The ratio of products from condensation of phthalic anhydride and *t*-Bu ester of 7-ACA depends on the reaction time. For example, if the mixture is heated only for 15 min, 160 mg of the phthalimido compound and about 4.34 g of the phthalamic acid is obtained.

t-*Butyl 7-phtalisoimido-3-acetoxymethyl-3-cephem-4-carboxylate* (**5e**). — A suspension of 1.32 g (4 mmol) of *t*-butyl ester of 7-ACA,[17] 660 mg of $NaHCO_3$ and 0.6 ml (4.4 mmol) of *o*-phthaloyl dichloride in 50 ml of dichloromethane was stirred at room temperature for 90 min. The solution was then washed successively with sat $NaHCO_3$ solution, 1 mol/dm^3 HCl, water and brine, dried, and evaporated in vacuo to dryness to provide 1.74 g (95%) of the isoimide as an amorphous solid; $[\alpha]_D$ — 56.9 °C (MeCN); NMR ($CDCl_3$) δ 1.55 (s, 9, *t*-Bu), 2.1 (s, 3, Ac), 3.38 and 3.7 (ABq, 2, J = 17 Hz), 4.93 and 5.18 (ABq, 2, J = 15 Hz), 5.2 (d, 1, J = 4.5 Hz), 5.82 (d, 1, J = 4.5 Hz), and 7.6—8.1 (m, 4, ArH).

Isomerization of iso-*imide.* — A mixture of 458 g (1 mmol) of *t*-butyl 7-phthal*iso*-imido-3-acetoxymethyl-3-cephem-4-carboxylate, 140 mg (2 mmol) of hydroxylamine hydrochloride, 170 mg (2 mmol) of sodium bicarbonate, 10 ml of THF and 2 ml of water was refluxed for 2—3 min, cooled, and evaporated. The residue was taken up in chloroform, washed with water and dried. After removal of the solvent, the product was recrystallized from dichloromethane and ether; m. p. 176—178 °C. The NMR spectrum is the same as that for the product prepared according to the method A.

p-*Nitrobenzyl 7-phthalimido-3-methyl-3-cephem-4-carboxylate* (**3f**). — To a suspension of 5.0 g (10 mmol) of *p*-nitrobenzyl 7-phthal*iso*imido-3-methyl-3-cephem-4--carboxylate in 100 ml of tetrahydrofuran was added 1.6 g of tetramethyl guanidinium azide. After the addition of azide in 1—2 min, everything was in solution. After stirring for 45 min, the mixture was evaporated to dryness, and the residue thereby obtained was dissolved in ethyl acetate (a part of the unreacted starting material was insoluble and was filtered off). The ethyl acetate solution was washed with 1 mol/dm^3 hydrochloric acid, water and brine. After drying the solvent was evaporated and 2.1 g of the titled imide was obtained. A sample for analysis was recrystallized from chloroform and cyclohexane, m. p. 192—193 °C; IR ($CHCl_3$) 5.60 and 5.78 μ; NMR ($CDCl_3$) δ 2.35 (s, 3), 3.0 and 3.74 (ABq, 2, J = 15 Hz), 5.18 (d, 1, J = 4.5 Hz), 5.4 (d, 2, J = 3.8 Hz), 5.75 (d, 1, J = 4.5 Hz) and 7.5—8.4 Hz (m, 9, ArH).

Anal. $C_{23}H_{17}N_3O_7S$ (479.39) calc'd.: C 57.62; H 3.57; N 8.76; O 23.36; S 6.69%
found: C 57.54; H 3.46; N 8.92; O 23.50; S 6.62%.

Hydrolysis of the Phthalimido Compounds to the Phthalamic Acids

7-(2-Carboxybenzamido)-3-methyl-3-cephem-4-carboxylic acid (**4a**). — To a solution of 7-phthalimido-3-methyl-3-cephem-4-carboxylic acid (**3a**) (3.44 g, 10 mmol) in 10 ml tetrahydrofuran at 0 °C, was added 80 ml of ice water and Na_2S—$9H_2O$ (5.3 g, 22 mmol). After 20 min at 0 °C 10 ml of 1 mol/dm^3 HCl was added the volume of the mixture was reduced in vacuo to ca. 100 ml. The aqueous solution was slurried with ethyl acetate (80 ml), and the pH was adjusted to 1.0 with conc. HCl. The organic layer was separated, washed with water (60 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated in vacuo to dryness to give 2.97 g (83%) of 7-(2-carboxybenzamido)-3-

-methyl-3-cephem-4-carboxylic acid as an amorphous solid; IR (KBr) 1772, 1730, 1720 and 1650 cm^{-1}; NMR ($DMSO_{d_6}$) δ 2.08 (s, 3, CH_3), 3.29 and 3.65 (ABq, 2, J = 19 Hz), 5.18 (d, 1, J = 4.5 Hz), 5.76 (dd, 1, J = 4.5 and 8.0 Hz), and 7.4—8.0 (m, 4, ArH).

Anal. $C_{16}H_{14}N_2O_6S$ (362.29) calc'd.: C 53.05; H 3.89; N 7.73%
found: C 52.91; H 4.17; N 7.52%.

General Method for Preparation of Esters of 7-(2-carboxybenzamido)-3-methyl--3-cephem-4-carboxylic Acid

A solution of 2 mmol of an ester of 7-phthalimido-3-methyl-3-cephem-4-carboxylic acid in 25 ml of THF and 8 ml of water was cooled in an ice water bath and then 660 mg of $Na_2S \cdot 9H_2O$ was added. After stirring for 15 min, 10 ml of water and 40 ml of ethyl acetate was added and the layers were separated. From the extract a small amount of unreacted starting material was obtained. The aqueous layer was acidified with 1 mol/dm^3 H_2SO_4 to pH 4.3, extracted twice with ethyl acetate. The extracts were combined, washed and dried. Upon evaporation of the solvent, the phthalamic acid was obtained either as amorphous solid or as crystals (see below).

After removal of Δ^3-acid at pH = 4.3, a solution was acidified to pH 2.0 and Δ^2-diacid, i. e., 7-(2-carboxybenzamido)-3-methyl-2-cephem-4-carboxylic acid was then extracted with ethyl acetate (2 × 30 ml). The ethyl acetate extracts were combined, washed with brine and dried ($MgSO_4$). A colorless crystalline product crystallized from the ethyl acetate layer during the evaporation in vacuo giving 7-(2-carboxybenzamido)-3-methyl-2-cephem-4-carboxylic acid; m. p. 196—198 °C (dec); IR (KBr) 1773, 1700, and 1658 cm^{-1}; NMR ($DMSO_{d_6}$) δ 1.88 (s, 3, CH_3), 4.64 (s, 1, C_4-H), 5.15 (d, 1, J = 4.0 Hz), 5.5 (dd, 1, J = 4.0 and 8.0 Hz), 6.15 (s, 1, C_2-H) and 7.4—8.0 (m, 4, ArH).

Anal. $C_{16}H_{14}N_2O_6S$ (362.29) calc'd.: C 53.03; H 3.89; N 7.73; S 8.85%
found: C 52.76; H 3.85; N 7.68; S 8.77%.

The following esters were prepared by the general method described above:

Methyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**4b**) was isolated in 80% yield as an amorphous colorless solid. Recrystallization from acetone gave an analytical sample; m. p. 182—184.5 °C (dec); IR (KBr) 1768, 1630, 1610 (shoulder) and 1665 cm^{-1}; NMR ($CDCl_3/DMSO_{d_6}$) δ 2.08 (s, 3, CH_3), 3.12 and 3.52 (ABq, 2, J = 17 Hz), 3.8 (s, 3, CH_3 ester), 5.06 (d, 1, J = 4.5 Hz), 5.86 (dd, 1, J = 4.5 and J = 8.0 Hz) and 7.4—8.0 (m, 4, ArH).

Anal. $C_{17}H_{16}N_2O_6S$ (376.31) calc'd.: C 54.25; H 4.28; N 7.44; S 8.52%
found: C 53.98; H 4.18; N 7.73; S 8.58%.

t-*Butyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate* (**4a**) was obtained in 84% yield and it was recrystallized from chloroform/cyclohexane; m. p. 178—179 °C IR (nujol) 1770, 1735, and 1680 cm^{-1}; NMR ($CDCl_3$ + $DMSO_{d_6}$) δ 1.5 (s, 9, t-Bu), 2.1 (s, 3, CH_3), 3.2 and 3.5 (ABq, 2, J = 18 Hz), 5.02 (d, 1, J = 4.5 Hz), 5.82 (dd, 1, J = 4.5 and 9 Hz), and 7.4—8 (m, H, ArH).

Anal. $C_{20}H_{22}N_2O_6S$ (418.39) calc'd.: C 57.40; H 5.30; N 6.69; O 22.94; S 7.66%
found: C 57.70; H 5.20; N 6.52; O 22.72; S 7.53%.

The identical (NMR, IR, m. p.) substance was also obtained in 94% yield from phthalic anhydride and t-butyl ester of 7-ADCA.

p-*Methoxybenzyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate* (**4d**) was obtained in 68% yield as amorphous solid, $[\alpha]_D$ + 85.6 ° (MeCN); IR ($CHCl_3$), 1781, 1740 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.08 (s, 3, CH_3), 3.1 and 3.43 (ABq, 2, J = 17 Hz), 3.79 (s, 3, CH_3), 5.0 (d, 1, J = 4.5 Hz), 5.1 (s, 2, CH_2) 5.8 (dd, 1, J = 4.5 Hz), 6.75—7.6 (m, 8).

Anal. $C_{24}H_{22}N_2O_7S$ (482.43) calc'd.: C 59.74; H 4.60; N 5.81; O 23.21; S 6.65%
found: C 59.81; H 4.32; N 6.07; O 23.34; S 6.51%.

p-*Nitrobenzyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate* (**4f**) was isolated in 30% yield. A sample was recrystallized from dioxane/water and colorless

crystals melted at 192—193 °C; NMR ($DMSO_{d_6}$) δ 2.04 (s, 3, CH_3), 3.35 and 3.68 (ABq, 1, J = 18 Hz), 5.2 (d, 1, J = 4 Hz, H-6), 5.4 (s, 2, CH_2), 5.8 (dd, 1, J = 4.5 and 9 Hz), 8 (m, 8, ArH).

Anal. $C_{23}H_{19}N_3O_8S$ (497.41) calc'd.: C 55.53; H 3.85; N 8.45; O 25.73; S 6.45%
found: C 55.67; H 3.94; N 8.49; O 25.89; S 6.47%.

The subsequent acidification of the aqueous solution to pH = 2.0 and extraction with ethyl acetate resulted in the isolation of *p*-nitrobenzyl 7-(2-carboxybenzamido)--3-methyl-2-cephem-4-carboxylate acid in 24% yield.

p-*Methoxybenzyl 6-(2-carboxybenzamido)penicillanate* (**9b**). — To a solution of *p*-methoxybenzyl 6-phthalimido penicillanate (**8b**) (2.33 g, 5 mmol) in 50 ml tetrahydrofuran at 0 °C were added 1.35 g (~ 5.5 mmol) of $Na_2S \cdot 9H_2O$ and 50 ml of ice water. After 12 min at 0 °C, 5 ml of 1.0 mol/dm³ HCl were added, and the volume of the mixture was reduced in vacuo to about 50 ml. The mixture was washed with two 50 ml portions of ethyl acetate. The pH of the aqueous layer was adjusted to 4.1 with conc. HCl and then was extracted with 35 ml ethyl acetate. The ethyl acetate extract was washed with brine and dried over $MgSO_4$. Evaporation in vacuo to dryness gave 2.35 g of *p*-methoxybenzyl 6-(2-carboxybenzamido)penicillanate as a colorless foam: NMR ($CDCl_3$) δ 1.36 (s, 3), 1.53 (s, 3), 3.79 (s, 3, OCH_3), 4.38 (s, 1, H-3), 5.08 (s, 2, CH_2), 5.5—5.83 (m, 2, β-lactam H), 6.67—8.0 (m, 8, ArH), and 10.5 (broad s, 1, COOH).

Benzhydryl 6-(2-carboxybenzamido)penicillanate (**9a**). — To a solution of benzhydryl 6-phthalimido penicillanate (**8a**) (2.56 g, 5 mmol) in 50 ml tetrahydrofuran at 0 °C were added 1.35 g (~ 5.5 mmol) $Na_2S \cdot 9H_2O$ and 50 ml ice water. After 10 min at 0 °C 5 ml of 1.0 mol/dm³ HCl were added, and the volume of the mixture was reduced in vacuo to ~ 50 ml. After washing the mixture with two 50 ml portions of ethyl acetate, the pH of the aqueous layer was adjusted to 4.0 with conc. HCl and then extracted with 50 ml ethyl acetate. The ethyl acetate layer was washed with brine and dried over $MgSO_4$. Evaporation in vacuo gave 850 mg of benzhydryl 6-(2-carboxybenzamido)penicillanate as a colorless foam.

t-*Butyl 7-(2-carboxybenzamido)-3-acetoxymethyl-3-cephem-4-carboxylate* (**4e**). To a solution of 458 mg (1 mmol) of *t*-butyl 7-phthalimido-3-acetoxymethyl-3--cephem-4-carboxylate (**3e**) in 10 mol of THF, cooled in an ice water bath, was added 1.1 ml of 1 mol/dm³ NaOH. After stirring for 5 min, 10 ml of water and 30 ml of ethyl acetate were added. From the organic layer 70 mg of a starting material were recovered. The aqueous portion was acidified to pH 4.0, and the acid extracted with ethyl acetate. After workup, 330 mg (83%) of the desired phthalamic acid was obtained: $[\alpha]_D$ +26.37° (MeCN) λ_{EtOH} 260 mμ (ε 8,800); IR ($CHCl_3$) 1785, 1730 and 1685 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9, *t*-Bu), 2.05 (s, 3, Ac), 3.3 and 3.6 (ABq, 2, J = 17 Hz), 4.72 and 5.2 (ABq, 2, J = 14 Hz), 4.98 (d, 1, J = 4.5 Hz), 5.9 (dd, 1, J = 4.5 and 9 Hz), and 7.5—8 (m, 4. ArH).

Conversion of the Phthalamic Acid to the iso-Imide

7-Phthalisoimido-3-methyl-3-cephem-4-carboxylic acid (**5a**). — To a solution of 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylic acid (**4a**) (376 mg, 1 mmol) in 15 ml of anhydrous tetrahydrofuran at room temperature was added sodium bicarbonate (420 mg, 5 mmol), and trifluoroacetic anhydride (0.33 ml, 2.25 mmol). After 10 min the reaction mixture was filtered and the filtrate evaporated to dryness. The product was taken up in ~ 10 ml 5% sodium bicarbonate solution and washed with ethyl acetate (15 ml). The pH of the aqueous solution was adjusted to 2.4 with 1 mol/dm³ HCl in the presence of ethyl acetate (20 ml). The organic layer was separated, washed with brine (20 ml), dried ($MgSO_4$), and evaporated in vacuo to dryness giving 7-phthalisoimido-3-methyl-3-cephem-4-carboxylic acid (240 mg, 67%) as a cream colored amorphous solid: m. p. 179—180 °C (dec); IR (KBr) 1818, 1770, 1731, and 1700 cm^{-1}; NMR (D_2O/HCO_3^-) δ 2.03 (s, 3, CH_3), 3.20 and 3.78 (ABq, 2, J = 18 Hz), 5.44 (d, 1, J = 4 Hz), 5.84 (d, 1, J = 4 Hz) and 7.4—8.0 (m, 4, ArH).

Anal. $C_{16}H_{12}N_2O_5S$ (344.27) calc'd.: C 55.81; H 3.51; N 8.14; O 23.23; S 9.31%
found: C 55.97; H 3.62; N 8.15; O 23.18; S 9.12%

Methyl 7-phthalisoimido-3-methyl-3-cephem-4-carboxylate (**5b**) prepared in 89% yield with trifluoroacetic anhydride as described in the previous experiment. Recry-

stallization from acetone gave 1.44 g (80%) methyl 7-phthal*iso*imido-3-methyl-3--cephem-4-carboxylate; m. p. 191—193 °C; IR (KBr) 1798, 1771, 1730, and 1710 cm^{-1}; NMR ($CDCl_3$) δ 2.19 (s, 3, CH_3), 3.19 and 3.60 (ABq, 2, J = 18 Hz), 3.85 (s, 3, CH_3 ester), 5.13 (d, 1, J = 4.5 Hz), 5.80 (d, 1, J = 4.5 Hz), and 7.6—8.28 (m, 4H, ArH).

Anal. $C_{17}H_{14}N_2O_5S$ (358.30) calc'd.: C 56.98; H 3.94; N 7.82; O 22.32; S 8.95%
found: C 56.83; H 3.83; N 7.81; O 22.50; S 8.94%

t-*Butyl 7-phthal*isoimido-3-methyl-3-cephem-4-carboxylate (**5c**)

A. *Ethyl chloroformate method.* — A mixture of 4.18 g (10 mmol) of t-butyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate, (**4c**) 40 ml of dry tetrahydrofuran and 1.39 ml (10 mmol) of triethylamine was cooled with an ice-salt bath. A solution of 1.0 ml (10.5 mmol) of ethyl chloroformate in 10 ml of dry THF was added and a mixture was stirred and cooled for 20 min. Stirring at room temperature was continued for an additional 20 min. After the precipitated salt ($Et_3N \cdot HCl$) was filtered, the filtrate was evaporated to dryness, and the obtained residue was dissolved in ethyl acetate and washed with water and brine. The solution was heated to the boiling point, cooled, and the solvent was evaporated. The residue (3.93 g or 98%) was a pure *iso*imide. A sample (1.0 g) was recrystallized from acetonitrile (5 ml) as silky needles (570 mg) m. p. 179—180 °C; $[\alpha]_D$ —128.7° (MeCN); IR (KBr) 1810, 1775, 1730 and 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9, *t*-Bu); 2.15 (s, 3, CH_3); 3.18 and 3.59 (ABq, 2, J = 18 Hz), 5.15 (d, 1, J = 4.5 Hz), 5.18 (d, 1, J = 4.5 Hz), and 7.65—8.05 (m, 4, ArH).

Anal. $C_{20}H_{20}N_2O_5S$ (400.38) calc'd.: C 59.96; H 5.03; N 7.00; S 8.01%
found: C 59.66; H 4.74; N 7.40; S 7.87%

B. *Dicyclohexylcarbodimide method.* — To a solution of *t*-butyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**4c**) (418 mg, 1 mmol) in 15 ml methylene chloride at room temperature was added dicyclohexylcarbodimide (206 mg, 1 mmol). After 1 h the reaction mixture was filtered and the filtrate evaporated in vacuo to dryness. The product was taken up in 20 ml ethyl acetate and washed successively with 1 mol/dm^3 HCl, 10% $NaHCO_3$ soln, and brine, dried ($MgSO_4$) and evaporated in vacuo to dryness to give 360 mg (90%) of a colorless amorphous solid. The NMR spectrum as well as all other physical chemical data agreed with that of the phthal*iso*imide prepared via ethylchloroformate/Et_3N.

p-*Methoxybenzyl 7-phthal*isoimido-3-methyl-3-cephem-4-carboxylate (**5d**) was prepared according to the ethyl chloroformate method. λ_{max} (EtOH) 265 mμ (ε 8,800); IR ($CHCl_3$) 1820, 1785, 1735, and 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (s, 3, CH_3), 3.15 and 3.55 (ABq, 2, J = 18 Hz), 4.00 (s, 3, CH_3), 5.18 (d, 1, J = 4.5 Hz), 5.3 (s, 2, CH_2), 5.78 (d, 1, J = 4.5 Hz), and 6.8—8 (m, 8, ArH).

Anal. $C_{24}H_{20}N_2O_6S$ (464.42) calc'd.: C 62.06; H 4.34; N 6.03; O 20.67; S 6.90%
found: C 62.18; H 4.34; N 6.26; O 20.66; S 6.98%

p-*Methoxybenzyl 6-phthal*isoimido *penicillanate* (**10b**). Ethyl chloroformate (0.2 ml, 2 mmol) was added to a solution of p-methoxybenzyl 6-(2-carboxybenzamido) penicillanate (**9b**) (968 mg, 2 mmol) and triethylamine (0.27 ml, 2 mmol) in 15 ml of tetrahydrofuran at 0 °C. After 15 min at 0 °C, the mixture was allowed to warm to room temperature, filtered, and the filtrate evaporated in vacuo to dryness. The crude product was taken up in 20 ml ethyl acetate and was washed successively with 10% $NaHCO_3$, water, and brine. After drying over $MgSO_4$, the ethyl acetate solution was evaporated in vacuo to dryness to give *p*-methoxybenzyl 6-phthal*iso*imido penicillanate as a light yellow foam: NMR ($CDCl_3$) δ 1.40 (s, 3), 1.63 (s, 3), 3.84 (s, 3, OCH_3), 4.52 (s, 1, 3-H), 5.15 (s, 2, CH_2), 5.64 (dd, 2, J = 4.0 Hz, azetidinone H), 6.85—8.20 (m, 8, ArH).

*Benzhydryl 6-phthal*isoimido *Penicillanate* (**10a**)

A. *Using trifluoroacetic anhydride.* — To a solution of 530 mg (1 mmol) of benzhydryl 6-(2-carboxybenzamido)penicillanate (**9a**) in 10 ml dry dioxane were added 0.14 ml (1 mmol) of triethylamine and 0.15 ml (1 mmol) of trifluoroacetic anhydride. After 10 min at room temperature the yellow reaction mixture was poured into 50 ml

of ice water (plus about 20 g ice). After the ice in the aqueous mixture melted, the light yellow precipitate was filtered giving 290 mg (after drying), of a yellow amorphous solid. The NMR spectrum was consistent for benzhydryl 6-phthal*iso*imido penicillanate: NMR ($CDCl_3$) δ 1.28 (s, 3), 1.65 (s, 3), 4.63 (s, 1, H-3), 5.70 (dd, 2, J = 4.0, azetidinone H), 7.0 [s, 1, $(C_6H_5)_2CH$] and 7.18—8.15 (m, 14, ArH).

B. *Using* N,N'-*dicyclohexylcarbodiimide.* — To a solution of 265 mg (0.5 mmol) benzhydryl 6-(2-carboxybenzamido)penicillanate in 7 ml of methylene chloride were added 102 mg (0.5 mmol) of *N,N'*-dicyclohexylcarbodiimide. After 1/2 h at room temperature the reaction mixture was filtered, and the filtrate was evaporated in vacuo to dryness. The NMR spectrum showed the crude product to be a clean sample of benzhydryl 6-phthal*iso*imido penicillanate (**10a**).

p-*Nitrobenzyl 7-phthal*iso*imido-3-methyl-3-cephem-4-carboxylate* (**5f**)

A. *Ethyl chloroformate method.* — *p*-Nitrobenzyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**4f**) (10 g, 20 mmol) and 2.8 ml (20 mmol) of triethylamine was dissolved in 200 ml of dry THF. While the mixture was stirred and cooled at ice bath temperature, 2.0 ml (20 mmol) of ethyl chloroformate was added. Stirring was continued for 20 min in an ice bath for 10 min at room temperature. The precipitate ($Et_3N \cdot HCl$) was filtered and the filtrate was evaporated to dryness to provide 4.6 g of a crude product which was recrystallized from acetonitrile as long chlorless needles: m. p. 204—205 °C; IR (KBr) 1821, 1785, 1730 and 1710 cm^{-1}.

Anal. $C_{23}H_{17}N_3O_7S$: (479.39) calc'd.: C 57.62; H 3.57; N 8.76; O 23.36; S 6.69%
found: C 57.42; H 3.53; N 8.99; O 23.64; S 6.66%

B. *Trifluoroacetic anhydride method.* — The solution of 1.0 g (2 mmol) of *p*-nitrobenzyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**4l**) and 0.34 ml (2.6 mmol) of triethylamine in 25 ml of dioxane was cooled in an ice water bath. While the mixture was stirred 0.36 ml (2.6 mmol) of trifluoroacetic anhydride was added. After 30 min, 10 ml of water was added, and the precipitated *iso*imide was filtered and dried: 840 mg (87%). The product was identical (IR, m. p.) to material prepared by method A.

Dephthaloylation of iso-*Imide by Hydrazinolysis*

7-Amino-3-methyl-3-cephem-4-carboxylic acid (**6a**). — To a suspension of 7-phthal*iso*imido-3-methyl-3-cephem-4-carboxylic acid (**5a**) (172 mg, 0.5 mmol) in tetrahydrofuran (7 ml) at 0 °C was added anhydrous hydrazine (0.032 ml, 1 mmol). After 7 min 1 mol/dm^3 HCl (2.5 ml) and water (2.5 ml) was added. The mixture was heated on a steam bath for 10 min, cooled and evaporated in vacuo to a volume of ca. 5 ml. The aqueous solution was filtered and the pH of the filtrate was adjusted to 3.7 with 5% sodium bicarbonate solution. After 15 min the solution was filtered to provide 73 mg (68%) of 7-amino-3-methyl-3-cephem-4-carboxylic acid. Spectral data as well as tlc data showed the product to be identical with an authentic sample of 7-ADCA.

Methyl 7-amino-3-methyl-3-cephem-4-carboxylate hydrochloride (**6b**). — Anhydrous hydrazine (0.053 ml, 97%, 1.6 mmol) was added to a suspension of methyl 7-phthal*iso*imido-3-methyl-3-cephem-4-carboxylate (**5b**) (570 mg, 1.6 mmol) in 15 ml tetrahydrofuran at 0°C. After 10 min at 0° the mixture was evaporated in vacuo to dryness. The resulting product was taken up in 3 ml tetrahydrofuran and 2.3 ml 1 mol/dm^3 HCl, heated on a steam bath for 5 min, and allowed to cool slowly to room temperature. Filtration gave 210 mg of a colorless crystalline product identified as phthalhydrazide (m. p. 339—343 °C). The filtrate (volume ~ 10 ml from washing of precipitate) was then evaporated in vacuo to a volume of ca. 5 ml. A gummy material which had formed on the walls of the flask was washed with 5 ml of water. The washings were combined with the remaining filtrate from above and evaporated in vacuo to dryness to give a light yellow amorphous product (260 mg, 62%). Thin layer chromatography showed only minor impurities. An analytical sample was obtained by recrystallization from ethanol/diethyl ether: m. p. 173—179 °C (dec); IR (KBr) 1770 and 1734 cm^{-1}; NMR ($DMSO_{d6}$) δ 2.18 (s, 3, CH_3), 3.62 (broad s, 2, methylene), 3.78 (s, 3, CH_3 ester), 5.06 (d, 1, J = 4.5 Hz) and 5.21 (d, 1, J = 4.5 Hz).

Anal. $C_9H_{13}N_2O_3SCl$ (264.74) calc'd.: C 40.82; H 4.95; N 10.58; S 12.11; Cl 13.39%
found: C 40.83; H 4.78; N 10.84; S 12.05; Cl 13.49%

The corresponding free amine was prepared by adjusting the pH of an aqueous solution of the prepared hydrochloride to 8.0 with sodium bicarbonate and extracting with ethyl acetate. When dried ($MgSO_4$), the ethyl acetate solution was evaporated to dryness to give a light yellow resinous product identified as methyl 7-amino-3--methyl-3-cephem-4-carboxylate: NMR ($CDCl_3$) δ 2.11 (s, 3, CH_3), 2.54 (broad s, 2, NH_2), 3.13 and 3.56 (ABq, 2, $J = 18$ Hz), 3.83 (s, 3, CH_3 ester), 4.69 (d, 1, $J = 4.6$ Hz) and 4.93 (d, 1, $J = 4.6$ Hz).

t-*Butyl 7-amino-3-acetoxymethyl-3-cephem-4-carboxylate* (**6e**). — To a solution of 916 mg (2 mmol) of *t*-butyl 7-phthal*iso*imido-3-acetoxymethyl-3-cephem-4-carboxylate (**5e**) in 15 ml of dry THF, cooled in an ice water bath, was added 0.078 ml of anhydrous hydrazine. The mixture was stirred for 5 min and the concentrated to a volume of 5 ml. After 3 ml of 1 mol/dm³ HCl was added, the mixture was refluxed for 2—3 min and then cooled to room temperature. The precipitated phthalhydrazide was filtered, and the filtrate was evaporated in vacuo to dryness to provide 410 mg (55%) of the hydrochloride salt. Conversion to the free amine was accomplished with $NaHCO_3$ in accordance with the procedure discussed in the ferogoing example. M. p., IR and NMR spectra of the free amine were in agreement with an authentic sample prepared according to the method of R. J. Stedman.[17]

t-*Butyl 7-(2-thienylacetamido)-3-acetoxymethyl-3-cephem-4-carboxylate* (**7a**). — To a solution of 1.37 g (3 mmol) of *t*-butyl 7-phthal*iso*imido-3-acetoxymethyl-3-cephem-4-carboxylate (**5e**) in 10 ml of dry THF, cooled in an ice water bath, was added 0.12 ml of anhydrous hydrazine. After stirring for 5 min, 0.75 ml of 2-thienylacetyl chloride was added. The mixture was refluxed for 8 min, cooled and evaporated in vacuo to dryness. The residue was dissolved in ethyl acetate and the solution washed successively with a $NaHCO_3$ solution, 1 mol/dm³ HCl, water and brine. The crude mixture was chromatographed over silica gel using a benzene/ethyl acetate gradient. Fractions 16—73 were collected giving 340 mg of *t*-butyl ester of cephalothin: $[\alpha]_D$ + + 40.0° (MeCN); λ_{max} (EtOH) 238 and 262 mμ (ε 14,200 and 8,300); IR ($CHCl_3$) 1785, 1740, 1730 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9, *t*-Bu), 2.1 (s, 3, CH_3), 3.25 and 3.6 (ABq, 2, $J = 17$ Hz), 3.82 (s, 2, CH_2), 4.75 and 5.14 (ABq, 2, CH_2), 4.92 (d, 1, $J = 4.5$ Hz), 5.82 (dd, 1, $J = 4.5$ and 9 Hz), and 7.2 (m, 3, ArH).

Anal. $C_{20}H_{24}N_2O_6S_2$ (452.41) calc'd.: C 53.08; H 5.35; N 6.19; O 21.21; S 14.17%
found: C 52.84; H 5.10; N 6.30; O 21.46; S 13.92%.

t-*Butyl 7-amino-3-methyl-3-cephem-4-carboxylate* (**6c**). — To a stirred solution of 400 mg (1 mmol) of *t*-butyl 7-phthalisoimido-3-methyl-3-cephem-4-carboxylate (**5c**) in 15 ml of dry THF, cooled in an ice-water bath, 0.04 ml of anhydrous hydrazine was added; stirring was maintained for 5 min. The mixture was then acidified with 2.5 ml of 1 mol/dm³ HCl. After heating briefly to reflux, most of the THF was evaporated in vacuo. The precipitated phthalhydrazide was filtered, washed with 10 ml of water, and again filtered. The filtrate was evaporated to dryness. The hydrochloride salt (270 mg or 88% thereby obtained was converted to the free amino ester, a colorless solid: m. p. 118—120 °C; $[\alpha]_D$ + 76.8° (MeCN); λ_{max} (EtOH) 268 mμ (ε 6,350); IR ($CHCl_3$) 1790 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (s, 9, *t*-Bu), 2.1 (s, 3, CH_3), 3.17 and 3.64 (ABq, 2, $J = 18$ Hz) and 4.7 (d, 1, $J = 4.5$ Hz), and 4.93 (d, 1, $J = 4.5$ Hz).

Anal. $C_{12}H_{18}N_2O_3S$ (270.28) calc'd.: C 53.31; H 6.71; N 10.36; O 17.75; S 11.86%
found: C 53.35; H 6.45; N 10.12; O 18.05; S 12.09%.

p-*Methoxybenzyl 7-amino-3-methyl-3-cephem-4-carboxylate,* p-*toluene sulfonic acid salt* (**6a**). — To a solution of 190 mg (0.4 mmol) of *p*-methoxybenzyl 7-phthal*iso*-imido-3-methyl-3-cephem-4-carboxylate (**5a**) in 10 ml of dry THF at room temperature was added 0.017 ml of anhydrous hydrazine. The mixture was stirred for 5 min and evaporated in vacuo to dryness. The residue was dissolved in 2.0 ml of 75% aqueous MeCN, 90 mg of *p*-tulenesulfonic acid monohydrate was added, and after short reflux the expected phthalhydrazide started to precipitate. After cooling to room temperature, the precipitate was filtered, the filtrate was evaporated, and the residue thereby obtained was triturated with ether. Yield 190 mg. This material was identical with the salt described by Chauvette et al.[19]

p-*Nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate,* p-*toluene sulfonate salt* (**6f**). — To a solution of 960 mg (2 mmol) of *p*-nitrobenzyl 7-phthal*iso*imido-3-methyl-3--cephem-4-carboxylate (**5f**) in 30 ml of dry THF, cooled in an ice water bath, was added 0.075 ml of anhydrous hydrazine. The mixture was stirred for 5 min and thereafter ca. 20 ml of the solvent was evaporated on a rotavapor; 4 ml of 1 mol/dm³ HCl was then added and the acidified mixture was heated on a steam bath for 5 min. The mixture was allowed to cool to room temperature for 30 min, and the precipitated phthalhydrazide (m. p. 340—343 °C) was filtered. The filtrate was evaporated to dryness to provide 750 mg (98%) of the hydrochloride salt of 7-ADCA *p*-nitrobenzyl ester, which was converted to the *p*-TsOH salt by standard procedure. A sample was recrystallized from methanol-ether: m. p. 170—174 °C (dec); NMR ($DMSO_{d6}$) δ 2.20 (s, 3, CH_3), 2.30 (s, 3, CH_3), 3.6 (s, 2, SCH_2), 5.22 (s, 2, CH_2 ester), 5.4 (s, 2, azetidinone H's), and 7.1—8.25 (m, 8, ArH); IR (KBr) 1780 (azetidinone CO) and 1730 cm^{-1} (ester CO).

Anal. $C_{22}H_{23}N_3O_8S_2$ (521.43) calc'd.: C 50.66; H 4.45; N 8.06; S 12.30%
found: C 51.03; H 4.27; N 8.19; S 11.91%.

Hydrazinolysis of isoimide with methylhydrazine. — To a suspension of 480 mg (1 mmol) *p*-nitrobenzyl 7-phthalisoimido-3-methyl-3-cephem-4-carboxylate (**5f**) in 25 ml dry tetrahydrofuran at 0 °C was added 0.054 ml (1 mmol) methylhydrazine. After 15 min at 0 °C the reaction mixture was evaporated in vacuo to dryness. The resulting product was dissolved in 15 ml chloroform and stirred for 1 h at room temperature and then evaporated in vacuo to dryness. To the resulting colorless product was added 6 ml 75% aqueous acetonitrile and 190 mg (1 mmol) *p*-toluenesulfonic acid monohydrate. The mixture was warmed on the steam bath for ~ 1 min, cooled and filtered to give 158 mg *N*-methylphthalhydrazide (**8**) (m. p. 244—245 °C). Evaporation of the filtrate in vacuo gave 500 mg (~ 93%) of a white amorphous solid which was identical to an authentic sample of *p*-nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate, *p*-toluenesulfonate salt (**6f**) (by TLC and NMR).

p-*Nitrobenzyl 7-phenylacetamido-3-methyl-3-cephem-4-carboxylate* (**7b**). — To a suspension of *p*-nitrobenzyl 7-phthalisoimido-3-methyl-3-cephem-4-carboxylate (**5f**) (480 mg, 1 mmol) in tetrahydrofuran at 0 °C was added anhydrous hydrazine (0.03 ml, 1.06 mmol). After 10 min the mixture was evaporated to dryness. The product was taken up in acetone (15 ml) and tetrahydrofuran (15 ml) and phenylacetyl chloride (0.28 ml, 2.2 mmol) was added. After refluxing for 30 min the mixture was cooled and evaporated in vacuo to dryness. The product was taken up in chloroform (50 ml) and washed successively with 1 mol/dm³ HCl (30 ml), 10% sodium bicarbonate (40 ml) and brine (40 ml), dried ($MgSO_4$) and evaporated in vacuo to dryness. The colorless product was slurried with ethyl acetate (12 ml). Filtration gave *p*-nitrobenzyl 7-phenylacetamido-3-methyl-3-cephem-4-carboxylate (280 mg, 60%). Recrystallization from ethyl acetate gave an analytical sample: m. p. 227—230 °C; IR (KBr) 1772, 1732 and 1652 cm^{-1}; NMR ($CDCl_3/DMSO_{d6}$) δ 2.17 (s, 3, CH_3), 3.23 and 3.54 (ABq, 2, J = 17 Hz), 3.62 (s, 2, side chain CH_2), 4.98 (d, 1, J = 4.5 Hz), 5.39 (s, 2, ester CH_2), 5.60 (dd, 1, J = = 4.5 and 8.0 Hz), 7.34 (s, 5, ArH) and 7.90 (m, 4, ArH).

Anal. $C_{23}H_{21}N_3O_6S$ (467.42) calc'd.: C 59.09; H 4.53; N 8.99; O 20.53; S 6.86%
found: C 58.92; H 4.24; N 9.21; O 20.40; S 6.64%.

Benzhydryl 6-aminopenicillanate (**11a**). — To a solution of 1 mmol benzhydryl 6--phthal*iso*imido penicillanate (**10a**) in 35 ml of dry tetrahydrofuran at — 76 °C was added a solution of 0.053 ml (1 mmol) of methylhydrazine in 5 ml tetrahydrofuran. The solution was then removed from the dry ice-acetone bath and was allowed to warm to room temperature over a 1 h period. The reaction mixture was evaporated in vacuo to dryness, and the product residue was taken up in 15 ml $CHCl_3$. The mixture was allowed to stand at room temperature for 1 h during which time methylphthalhydrazide (m. p. 243—245 °C) precipitated. Filtration and evaporation in vacuo of the filtrate gave a light colored foam which was taken up in 20 ml of ethyl acetate and extracted twice with 10 ml of 0.05 mol/dm³ HCl. The aqueous acidic extracts were combined and added dropwise to a stirred slurry of 25 ml of ethyl acetate and 25 ml of 10% $NaHCO_3$ solution. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Evaporation gave a colorless foam. Thin layer chromatography (TLC) and the NMR spectrum of the foam are consistent with the structure of the title compound.

p-*Methoxybenzyl 6-aminopenicillanate* (**11b**). — To a solution of 480 mg (1 mmol) of *p*-methoxybenzyl 6-phthalisoimido (**10b**) penicillanate in 35 ml of dry tetrahydrofuran at — 76 °C was added a solution of 0.053 ml (1 mmol) of methylhydrazine in 5 ml tetrahydrofuran. The solution was then removed from the dry ice-acetone bath and was allowed to warm to room temperature over a 1 h period. The reaction mixture was evaporated in vacuo to dryness, and the product residue was taken up in 15 ml $CHCl_3$. The mixture was allowed to stand at room temperature for 1 h during which time methylphthalhydrazide (m. p. 243—245 °C) precipitated. Filtration and evaporation in vacuo of the filtrate gave a light colored foam which was taken up in 20 ml of ethyl acetate and extracted twice with 10 ml of 0.05 mol/dm³ HCl. The aqueous acidic extracts were combined and added dropwise to a stirred slurry of 25 ml of ethyl acetate and 25 ml of 10% $NaHCO_3$ solution. The organic layer was separated, washed with brine, and dried over $MgSO_4$. Evaporation in vacuo gave 200 mg (60%) of *p*-methoxybenzyl 6-aminopenicillanate as a colorless foam: NMR ($CDCl_3$) δ 1.42 (s, 3), 1.62 (s, 3), 3.85 (s, 3, OCH_3), 4.44 (s, 1, H-3), 4.57 (d, 1, J = 4.0 Hz, azetidinone H), 5.18 (s, 2, CH_2), 5.53 (d, 1, J = 4.0 Hz, azetidinone H) and 6.82—7.5 (m, 4, ArH); mass spec. *m/e* 336, M^+.

Benzhydryl 6-phenylacetamido penicillanate (**12a**). — To a solution of 512 mg of benzhydryl 6-phthal*iso*imido penicillanate (**10a**) in 40 ml of dry tetrahydrofuran at — 76 °C was added a solution of 0.05 ml of methylhydrazide in 5 ml of tetrahydrofuran. The solution was then removed from dry ice-acetone bath and was allowed to warm to room temperature. To this mixture a solution of 0.14 ml of phenylacetyl chloride in 5 ml of tetrahydrofuran was added and stirred at room temperature for 30 min and then the solvent was evaporated in vacuo to dryness. The crude product was purified by preparative thin layer chromatography (silica gel) using ethyl acetate : toluene (9 : 1) as a solvent. Compound **12** was obtained as a colorless foam: IR ($CHCl_3$) 1782, 1740 and 1672 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 3, Me), 1.5 (s, 3, Me), 3.62 (s, 2, CH_2Ph), 4.5 (s, 1, H-3), 5.6 (m, 2, azetidinone H), 6.66 (d, 1, J = 8 Hz, NH), 6.95 (s, 1, $CHPh_2$), 7.38 (br s, 15, arom. H); mass spec. *m/e* 500, M^+.

Anal. $C_{29}H_{28}N_2O_4S$ (500.53) calc'd.: C 69.58; H 5.64; N 5.60; S 6.40%.
found: C 69.35; H 5.51; N 5.49; S 6.21%.

Dephthaloylation of Phthalamic Acids via Mixed Anhydride

Methyl 7-amino-3-methyl-3-cephem-4-carboxylate hydrochloride (**6b**). — To a suspension of methyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**5b**) (752 mg, 2 mmol) in 35 ml of tetrahydrofuran at 0 °C was added triethylamine (0.28 ml, 2 mmol). After 15 min, ethyl chloroformate (0.2 ml, 2 mmol) was added, and then after one-half hr at 0 °C anhydrous hydrazine (0.07 ml 2.2 mmol) was added to the reaction mixture. After 15 min, the mixture was filtered, and the filtrate was evaporated in vacuo to dryness. The crude product was taken up in 20 ml of chloroform, refluxed for 90 min, and then allowed to stir at about 35 °C overnight. Filtration gave 180 mg of phthalhydrazide (m. p. 340—343 °C). The filtrate was evaporated to dryness in vacuo. The resulting crude product was taken up in 3 ml of 1 mol/dm³ HCl plus 2 ml water and washed with ethyl acetate (2 × 7 ml). Evaporation of the aqueous layer in vacuo gave a yellow amorphous solid which was recrystallized from ethanol/diethyl ether to give 115 mg of methyl 7-amino-3-methyl-3-cephem-4-carboxylate hydrochloride, m. p. 173—179 °C.

Anal. $C_9H_{13}N_2O_3SCl$ (264.74) calc'd.: C 40.82; H 4.95; N 10.58; S 12.11; Cl 13.39%
found: C 40.83; H 4.78; N 10.84; S 12.04; Cl 13.49%.

p-*Nitrobenzyl 7-amino-3-methyl-3-cephem-4-carboxylate* p-*toluene sulfonate salt* (**6f**). — A solution of 1.0 g (2 mmol) of *p*-nitrobenzyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**5f**) in 30 ml of dry tetrahydrofuran was cooled in an ice-salt bath, and 0.28 ml (2 mmol) of triethylamine and 0.20 ml (2 mmol) of ethyl chloroformate were added. After cooling and stirring for 20 min, 0.15 ml of 85% hydrazine hydrate was added, and stirring was continued for 10 min. The precipitated $Et_3N \cdot HCl$ salt was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in a mixture of 25 ml of ethyl acetate and 10 ml of water. The organic extract was separated from the aqueous and washed with $NaHCO_3$ solution, water, and brine. After drying, the solvent was evaporated. The residue was dissolved in 10 ml of

acetonitrile, and the solution was refluxed for 50 min and then cooled. To this solution 380 mg of *p*-toluenesulfonic acid hydrate and 2.5 ml of water were added, the precipitate (160 mg) was filtered, and most of the acetonitrile was evaporated from the filtrate. Upon cooling and scratching, crystallization began. Two hours later 680 mg (63%) of the title compound were collected. The purity of product was tested by thin layer chromatography (TLC) using silica plate and MeOH : benzene (1 : 3) system. A sample was recrystallized from methanol-ether, m. p. 170—174 °C; NMR ($DMSO_{d6}$) δ 2.20 (s, 3, CH_3), 2.30 (s, 3, CH_3), 3.6 (s, 2, SCH_2), 5.22 (s, 2, CH_2 ester), 5.4 (s, 2, azetidinone H's), and 7.1—8.25 (m, 8, ArH's); IR (KBr) 1780 (azetidinone CO) and 1730 cm^{-1} (ester CO).

Anal. $C_{22}H_{23}N_3O_8S_2$ (521.43) calc'd.: C 50.66; H 4.45; N 8.06; S 12.30%
found: C 51.03; H 4.27; N 8.19; S 11.91%.

p-*Nitrobenzyl 7-phenylacetamido-3-methyl-3-cephem-4-carboxylate* (**7b**). — To a suspension of *p*-nitrobenzyl 7-(2-carboxybenzamido)-3-methyl-3-cephem-4-carboxylate (**4f**) (462 mg, 1 mmol) in tetrahydrofuran at 0 °C was added triethylamine (0.14 ml, 1 mmol). After 15 min, ethyl chloroformate (0.1 ml, 2 mmol) was added, and then after 0.5 hr at 0 °C anhydrous hydrazine (0.03 ml, 1 mmol) was added to the reaction mixture. After 15 min, the mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was taken up in acetone (15 ml) and tetrahydrofuran (15 ml), and phenylacetyl chloride (0.13 ml, 1 mmol) was added. After refluxing for 30 min, the mixture was cooled and evaporated in vacuo to dryness. The product was taken up in chloroform (50 ml) and washed successively with 1 mol/dm^3 HCl (30 ml), 10% sodium bicarbonate (40 ml), and brine (40 ml), dried over $MgSO_4$, and evaporated in vacuo to dryness. The colorless product was slurried with ethyl acetate (12 ml). Filtration gave *p*-nitrobenzyl 7-phenylacetamido-3-methyl-3-cephem-4-carboxylate. Recrystallization from ethyl acetate gave an analytical sample: m. p. 227—230 °C.

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SAŽETAK

Deftaloilacija cefalosporina i penicilina koji sadržavaju ftalimid

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Izvedena je putem odgovarajućih ftaloizoimida deftaloilacija cefalosporina i penicilina koji sadržavaju ftalimid. Opisan je eksperimentalni postupak i mehanizam reakcije.

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Prispjelo 28. prosinca 1976.