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Mixed Anhydrides of Penicillinic and Cephalosporinic Acids with *N*-Acyl Carbamic Acid[1]

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Mixed anhydrides with penicillinic acids (*III*) were unstable and gave *N*-acyl, amides *IV*. Only *III* with butyrolactam was stable and reacted with alcohols to give esters *V*. All anhydrides with cephalosporinic acids (*VIII*) yielded symmetric anhydrides *IX*. Alcoholysis of *IX* gave cephalosporinic ester *X*, while aminolysis yielded amide. Formation of postulated isomeric mixed anhydride with O-imino carbonic acid ester XIIIb is discussed.

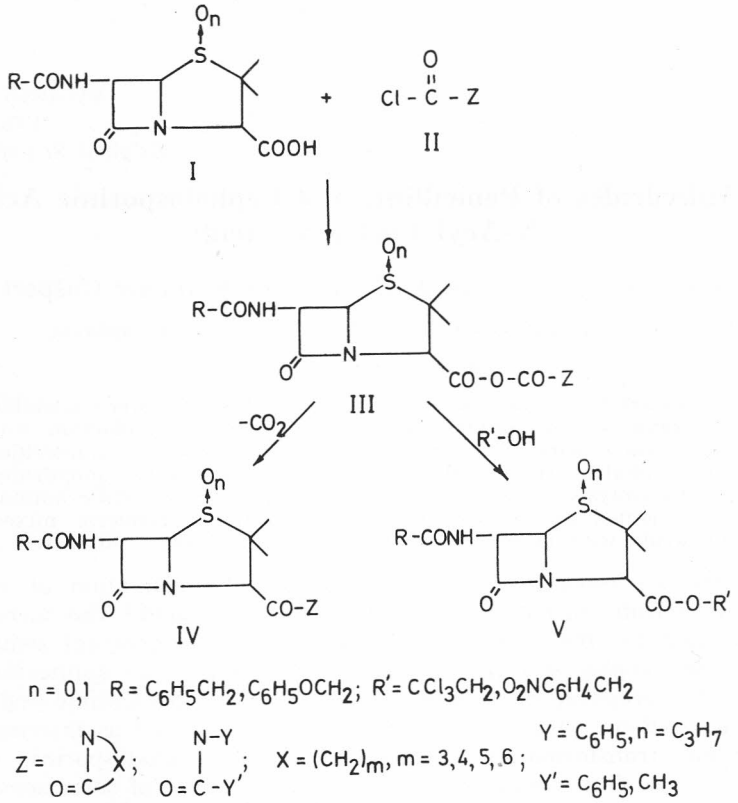
Recently we reported a new method for the activation of carboxylic acids by anhydride formation with *N*-acyl carbamic acid.[2] The successful use of this method for the preparation of some clinical important semisynthetic penicillins and cephalosporins[3] stimulated us to study the application of this method to the preparation of carboxy derivatives of penicillinic and cephalosporinic acids. Some of these derivatives have been used as intermediates in the chemical transformation of penicillins into cephalosporins, especially esters which also find a clinical application as pro drug of some semisynthetic penicillins like ampicillin (Pivampicillin, Bacampicillin).[4a,b,c]

In the present paper we wish to report the results of a study dealing with the reactivity of mixed anhydrides (*III*, *VIII*), preparation of some penicillinic and cephalosporinic acid derivatives (*IV*, *V*, *IX*, *X*) and discuss the formation of an isomeric mixed anhydride *XIIIb*. In the study of the reactivity of *III* and *VIII*, we tried not only to ascertain the reaction conditions which favour side reactions, but also to find a dependance of this reactions upon the nature of carboxylic and *N*-acyl carbamic acid group.

The mixed anhydrides *III* and *VIII* were prepared by a general method reported for the preparation of mixed anhydrides with *N*-acyl carbamic acid.[2] The necessary *N*-chlorocarbonyl intermediates (*II*, *VII*) may be obtained by the slightly modified method described in literature.[2] The penicillinic (*I*) or cephalosporinic (*VI*) acid was dissolved in an inert organic solvent in the presence of a tertiary base, cooled to 0 °C ,and *N*-chlorocarbonyl intermediate (*II* or *VII*) added with stirring.

The chemical and spectroscopic evidence for the anhydride structure RCO—O—CO—N(CO)X of the product, was considered in a previous publication.[2] It should be added here that the characteristic bands in the IR spectrum of mixed anhydride, *i. e.* a doublet in the carbonyl region at 1800—1820

Scheme I

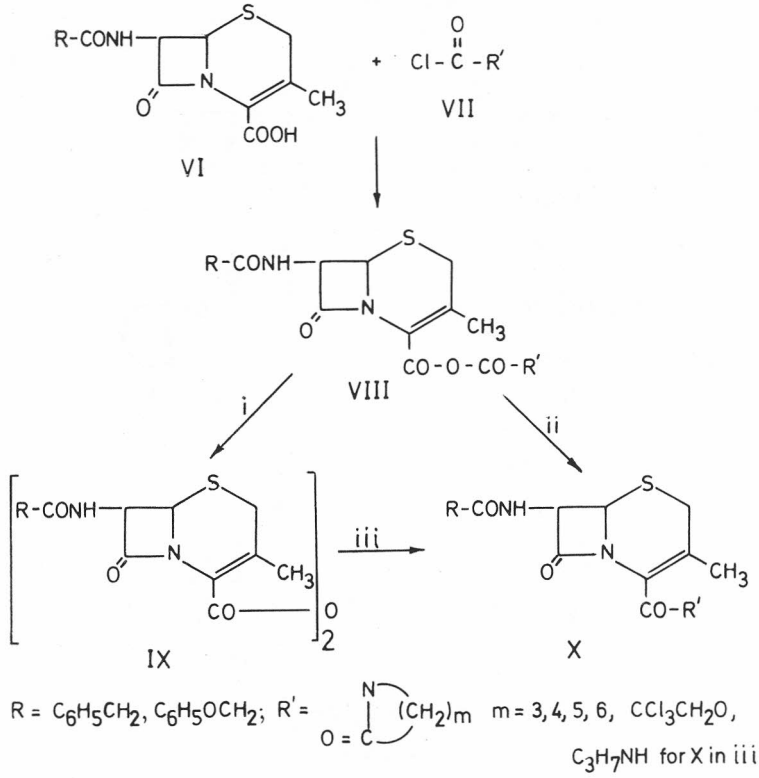


and 1740—1760 cm^{-1}, with a singlet of sec. amide carbonyl at 1690—1720 cm^{-1}, correspond to those reported for the acyl carbamic acid anhydrides RCO—O—CO—NHCOR′, prepared by the reaction of carboxylic acid with *N*-acyl isocyanates.[5]

In general, mixed anhydrides of the most carboxylic acids prepared so far, have been stable at 0 °C, and may be used in further reactions with nucleophiles. However, the mixed anhydrides *III* and *VIII* are so reactive that only one of *III* has been found to be sufficiently stable to be used for the preparation of esters. Alcoholysis of *III* (Z = N—CO—$(CH_2)_3$) with trichloroethanol or *p*-nitrobenzyl alcohol gave corresponding esters (*V*) in 80—85% yield. All other mixed anhydrides were less stable and underwent side reactions like decarboxylation (*IV*) or formation of a symmetric anhydride (*IX*).

The mixed anhydrides with penicillinic acids (*III*) start losing carbon dioxide even in the course of formation at 0 °C ,to yield *N*-acyl amides (*IV*) in high yield and purity. It makes them unsuitable for a reaction with nucleophiles, but usefull for the preparation of *N*-acyl amides. This side reaction was detected also by the mixed anhydrides of some other carboxylic acids, but only at more drastic reaction conditions, higher temperature and longer

Scheme II



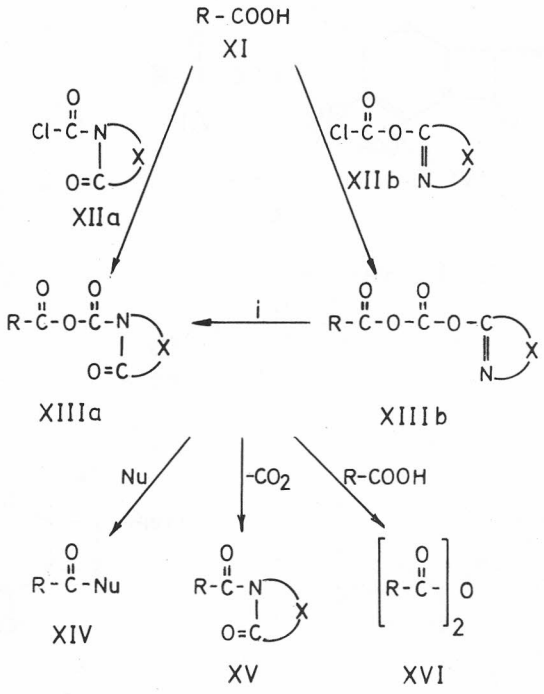
reaction time.[2] It follows that mixed anhydrides may be used as intermediates also for the preparation of other *N*-acyl amides.

This method may be convenient for the preparation of sensitive *N*-acyl amides, since the existing methods are more suitable for the simple ones. In general, they are prepared by heating the amides with acid chlorides or anhydrides; for the preparation of *N*-acetyl derivatives isopropenyl acetate or ketens have been used frequentlly.[6] Some penicillinic *N*-acyl amides have been obtained by Mumm's method, which consists in the interaction of a salt of carboxylic acid with imidoyl chloride.[7]

The mixed anhydrides of cephalosporinic acids (*VIII*) are so reactive that they gave symmetric anhydrides (*IX*) immediatelly after formation, which separated from the reaction solution in high yield and purity. A tendency of the mixed anhydrides to give symmetric anhydrides was detected also by some other carboxylic acids particularly when a symmetric anhydride was less soluble in the reaction solution than a mixed anhydride.[2]

The anhydride structure of the product *IX* was deduced from the chemical and spectroscopic data. Alcoholysis of *IX*, in the presence of pyridine

Scheme III



as catalyst, gave the corresponding ester *X* ($R' = CCl_3CH_2O$) and cephalosporinic acid *VI*. In the reaction with amine, *IX* the yielded corresponding amide *X* ($R' = C_3H_7NH$) and acid *VI*. The IR spectrum of *IX* had a characteristic doublet of carbonyl bands of unsaturated symmetric anhydride at 1790 and 1765 cm^{-1} and intensive C—O—C bands at 1132 and 1087 cm^{-1}.

Apparently, the reactivity of *III* and *VIII* depends more on the nature of the carboxylic than on the *N*-acyl carbamic acid part of the molecule. While *III* gave mostly *N*-acyl amides, *VIII* reacted to yield only symmetric anhydrides. It may be added that the reactivity of mixed anhydrides with *N*-acyl carbamic acid seems to be more specific than one prepared with carbonic acid esters; *VIII* /$R' = \underline{N—CO—(CH_2)_m}$/ gave only symmetric anhydrides *IX*, while *VIII* /$R' = CCl_3CH_2O$) gave symmetric anhydride *IX* and in part the ester *X* ($R' = CCl_3CH_2O$), due to partial decarboxylation.

Although the chemical and spectroscopic evidences for the mixed anhydride suggested the structure *XIIIa*, they are also consistent with the structure of an isomeric mixed anhydride with *O*-imino carbonic acid ester *XIIIb*. This isomeric anhydride, formed in the rection of *XI* with intermediate *XIIb*, may be postulated if *O*-chlorocarbonyl intermediate *XIIb* was present in the react-

ion product *XII*. On the other hand, the presence of *XIIb* in an intermediate *XII* may be plausible, due to the reaction of carbonyl dichloride with an imino form of lactams or *sec.* amides. Therefore, if the evidences could be obtained for the presence of *XIIb* in the reaction product *XII*, the formation of *XIIIb* may be plausible. One of the evidences for *XIIb* should appear in the IR spectrum of the reaction product XII. However, it was very difficult to distinguish in IR spectrum *N*-chlorocarbonyl structure from *O*-chlorocarbonyl one on the ground of the carbonyl band. Not only that the usuall bands of *N*- and *O*-chlorocarbonyl group are very close,[8,9] they also vary in the position, depending upon conjugation with C=N group or substitution with *N*-acyl group. Only the absence of the C=N band, which usually appears at 1690—1640 cm^{-1}, indicated that the isomer *XIIb* was not present in the reaction product *XII*. But it also can not be taken as evidence, since it is usually difficult to identify the presence of this band, because the intensity varies widely with the nature of the groups attached.[10]

It can be concluded that there is no indication for the formation of mixed anhydride with *O*-imino carbonic acid ester in the reaction conditions employed for the preparation of mixed anhydrides with *N*-acyl carbamic acid. In this connection it may be noted that the presence of *XIIIb* would be of no consequences for the reaction products otulined in scheme *III*. The isomer *XIIIb* would be very reactive and easilly rearrenge to *XIIIa* or would react on the way analogue to *XIIIa* to give the same products.

There are some analogues reported in literature which support this speculations.[11] Similar *O*-acyl intermediates have been postulated in the reaction of carboxylic acids with carbodiimides, cyanadimes or ketenimines. All attempts to isolate them failled, since they are all very reactive and easilly undergoe the O → N acyl migration to give stable *N*-acyl derivatives.

EXPERIMENTAL

Melting points are uncorrected.

The IR spectra were recorded on a Perkin-Elmer Infracord Model 257G. The UV spectra were recorded with a SP-8-100 Unicam spectrometer. The ^1H NMR spectra were taken with an EM-360 Varian spectrometer, unless otherwise stated, with TMS as internal standard. Chemical shifts are given in ppm (δ). Optical rotations were measured on Carl Zeiss polarimeter Polamat.

TLC was conducted on original plates (Merck, Kieselgel HF_{254}) followed by detection with iodine vapors and water or with UV absorption in solvent system:

(A) methylene chloride-ether (4 : 1)

(B) methylene chloride-ether-methanol (14 : 5 : 1).

Preparation of N-Penicilanoyl Lactams (IV)

N-6-Phenylacetamidopenicillanoyl butyrolactam (IV; R = $C_6H_5CH_2$, Z = N—CO—$(CH_2)_3$, n = O)

A solution of *N*-chlorocarbonyl butyrolactam (2.95 g, 20 mmol) in methylene chloride (50 ml) was added dropwise to a stirred suspension of benzylpenicillin potassium (7.4 g, 20 mmol) in methylene chloride (100 ml) and pyridine (1,6 g, 20 mmol) at 0 °C over a period of 10 minutes. The reaction mixture was warmed to 40 °C and stirred for additional 30 minutes without warming. The mixture was cooled to 5 °C, cold water added (50 ml) with stirring, the organic layer separated and washed with water. After drying ($MgSO_4$), the solvent was evaporated and the residue crystallized from a mixture of ethyl-acetate-ether-*n*-hexan.

Yield: 5.36 g (66.8%); m. p. 152—6 °C; $[\alpha]_D^{23}$ + 91° (c 0.5, CH_2Cl_2); R_f 0.35 (System A).

Anal. $C_{20}H_{23}N_3O_4S$ (401.47) calc'd.: C 59.83; H 5.77; N 10.47%
found: C 59.58; H 6.27; N 10.27%.

IR Spectrum (KBr): 3340(s), 2965(m), 1773(vs), 1738(s), 1680(vs), 1515(s), 1365(s), 1310(s), 1255(s), 1237(s), 1192(w), 1155(w), 920(m), 908(m), and 638(m) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 1.37 and 1.40 (2s, $2CH_3$), 1.75—2.32 (m, CH_2), 2.35—2.85 (m, CO—CH_2), 3.63 (s, Ph—CH_2), 3.50—4.0 (m, N—CH_2), 5.35—5.75 (m, C_5—H and C_6—H), 5.87 (s, C_3—H), 6.34 (d, J = 9 Hz, CONH), 7.37 (s, C_6H_5).

N-6-Phenylacetmidopenicillanoyl valerolactam (IV; R = $C_6H_5CH_2$, Z = N—CO—(CH_2)$_4$, n = 0)

A solution of *N*-chlorocarbonyl valerolactam (4 g, 25 mmol) in methylene chloride (50 ml) was added dropwise to a suspension of benzylpenicillin potassium (7.4 g, 20 mmol) in methylene chloride (100 ml) and pyridine (1.6 g, 20 mmol) with stirring at 0 °C over a period of 5 minutes and the reaction mixture stirred for 150 minutes. Cold water was added with stirring and the organic layer separated, washed with water (200 ml), dried ($MgSO_4$), filtered and the solvent evaporated. The residue was chromatographed over the silica gel column using the methylene chloride-ether gradient. The compound with R_f 0.47 (system A) was separated.

Yield: 5.8 g (70%); m. p. 183—5 °C; $[\alpha]_D^{23}$ + 150° (c 0.5, CH_2Cl_2); R_f 0.47 (System A).

Anal. $C_{21}H_{25}N_3O_4S$ (415.50), calc'd.: C 60.65; H 6.06; N 10.11; S 7.72%
found: C 60.47; H 6.37; N 10.25; S 7.40%

IR spectrum (KBr): 3350(m), 2960(m), 1775(s), 1680(vs), 1515(m), 1455(w), 1365(m), 1345(m), 1293(m), 1214(s), 1140(m), 720(m), 700(m) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 1.4 (s, $2CH_3$), 1.55—2.05 (m, $4CH_2$), 2.16—2.73 (m, CO—CH_2), 3.30—3.82 (m, N—CH_2), 3.57 (s, Ph—CH_2), 5.18—5.70 (m, C_5—H, C_6—H. C_3—H), 6.10 (d, J = 8 Hz, NH), 7.20 (s, $2C_6H_5$).

N-6-Phenylacetamidopenicillanoyl caprolactam (IV; R = $C_6H_5CH_2$, Z = N—CO—(CH_2)$_5$; n = O)

A solution of *N*-chlorocarbonyl caprolactam (3.7 g, 21 mmol) in methylene chloride (20 ml) was added, at 0 °C with stirring over a period of 10 minutes to a suspension of benzylpenicillin potassium (7.4 g, 20 mmol) and pyridine (1.6 g, 20 mmol) in methylene chloride (100 ml). The reaction mixture was stirred for 90 minutes at 0 °C, cold water (200 ml) added and the organic layer separated, washed with 5 M HCl (50 ml), water (2 × 100 ml) and dried ($MgSO_4$). After filtration, the solvent was evaporated and a frothy residue recrystallized from a mixture of ehylacetate-ether.

Yield: 6.6 g (77.2%); m. p. 163—5 °C; $[\alpha]_D^{23}$ + 181° (c 0.5, CH_2Cl_2); R_f 0.60 (System A).

Anal. $C_{22}H_{27}N_3O_4S$ (429.5), calc'd.: C 61.47; H 6.34; N 9.78%
found: C 61.72; H 6.63; N 9.84%.

IR spectrum (KBr): 3345(m), 2925(m), 1775(vs), 1678(vs), 1512(m), 1385(m), 1365(m), 1300(m), 1255(m), 1180(m), 1150(m), 965(m), 727(m), 705(m) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 1.4 and 1.42 (2s, $2CH_3$), 1.40—2.00 (m, $3CH_2$), 2.50—2.80 (m, CO—CH_2), 3.67 (s, Ph—CH_2), 3.70—4.00 (m, N—CH_2), 5.35—5.67 (m, C_5—H, C_6—H), 5.70 (s, C_3—H), 6.23 (d, J = 8 Hz, CO—NH), 7.38 (s, C_6H_5).

N-6-Phenylacetamidopenicillanoyl enantholactam (IV; R = $C_6H_5CH_2$, Z = N—CO—(CH_2)$_6$, n = O)

A solution of *N*-chlorocarbonyl enantholactam (3.8 g, 20 mmol) in methylene chloride (50 ml) was added at 0 °C to a suspension of benzylpenicillin potassium (7.4 g, 20 mmol) and pyridine (1.6 g, 20 mmol) in methylene chloride (100 ml). The

reaction mixture was stirred for 40 minutes at 0 °C, cold water (100 ml) added, stirred for 5 minutes, the organic layer separated and dried ($MgSO_4$). After evaporation of the solvent, a frothy residue was crystallized from a mixture of ethylacetate-ether.

Yield: 6.75 g (76%); m. p. 158—161 °C; $[\alpha]_D^{23}$ + 185.3° (c 0.5, CH_2Cl_2); R_f 0.50 (System A).

Anal. $C_{23}H_{29}N_3O_4S$ (443.55), calc'd.: C 62.27; H 6.59; N 9.47; S 7.72%
found: C 62.07; H 6.62; N 9.76; S 7.70%.

IR spectrum (KBr): 3400(vs,b), 2915(m), 1777(s), 1678(vs), 1510(m), 1375(s), 1337(w), 1295(m), 1250(m), 1205(s), 1130(m), 700(m) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 1.43 (s, $2CH_3$), 1.00—2.20 (m, $4CH_2$), 2.35—2.85 (m, CO—CH_2), 3.60 (s, Ph—CH_2), 3.60—4.30 (m, N—CH_2), 5.30—5.70 (m, C_3—H, C_5—H, C_6—H) 6.23 (d, J = 9 Hz, CO—NH), 7.34 (s, C_6H_5).

N-6-Phenoxyacetamidopenicillanoyl 1-oxide enentholactam (IV; R = $C_6H_5OCH_2$, Z = N—CO—$(CH_2)_6$, n = 1)

To a solution of phenoxyacetamidopenicillin-1-oxide (6.6 g, 18 mmol) and pyridine (1.6 g, 20 mmol) in methylene chloride (100 ml) a solution of *N*-chlorocarbonyl enantholactam (3.8 g, 20 mmol) in methylene chloride (50 ml) was added at 0 °C with stirring. The reaction mixture was stirred for 2 hours at 0 °C, cold water added, stirred for 5 minutes, the organic layer separated and washed with 1 M $NaHCO_3$ solution (100 ml), water (150 ml) and dried ($MgSO_4$). After evaporation of the solvent, a frothy product was obtained.

Yield: 6.9 g (81%); $[\alpha]_D^{23}$ + 75.3° (c 0.5, CH_2Cl_2); R_f 0.45 (System A).

Anal. $C_{23}H_{29}N_3O_6S$ (475.29), calc'd.: C 58.09; H 6.15; N 8.84; S 6.74%
found: C 58.30; H 6.28; N 8.43; S 6.95.%

IR spectrum (CH_2Cl_2): 3370(m), 2930(s), 1795(vs), 1685(vs), 1655(s,sh), 1600(m), 1515(s), 1495(s), 1440(m), 1370(m), 1230(s), 1205(s), 1125(m), 1065(m) cm^{-1}.

^1H NMR spectrum ($CDCl_3$). 1.34 and 1.80 (2s, $2CH_3$), 0.90—2.5 (m, $4CH_2$), 2.20—2.60 (m, CO—CH_2), 3.00—3.50 (m, N—CH_2), 4.50 (s, Ph—CH_2), 4.90 (s, C_3—H), 5.07 (d, J = 4 Hz, C_5—H), 6.03 (2d, J = 4 and 10 Hz, C_6—H), 6.40—7.50 (m, C_6H_5), 8.34 (d, J = 10 Hz, CONH).

Preparation of N-Penicillinyl sec. Amides (IV)

N-Phenyl-N-6-phenoxyacetamidopenicillanoyl acetamide (IV; R = $C_6H_5OCH_2$, Z = N(C_6H_5)—CO—CH_3, n = O)

To a solution of *N*-chlorocarbonyl acetanilide (0.98 g, 5 mmol) in toluene (10 ml) and pyridine (0.4 g, 5 mmol) phenoxymethylpenicillin (1.75 g, 5 mmol) was added. The mixture was stirred at 0 °C for 30 minutes, 0.1 M HCl (20 ml) added and the organic layer separated, washed with water (10 ml), 1 M $NaHCO_3$ solution (10 ml), water (10 ml) and dried ($MgSO_4$). After the solvent was evaporated, a frothy residue was chromatographed over the silica gel column using the methylene chloride-ether gradient. The compound with R_f 0.58 was separated.

Yield: 1.75 g (74%; m. p. 78—80 °C; $[\alpha]_D^{23}$ + 154.3° (c 0.5, CH_2Cl_2); R_f 0.58 (System A).

Anal. $C_{24}H_{25}N_3O_5S$ (476.5), calc'd.: C 61.66; H 5.40; N 8.99; S 6.85%
found: C 61.42; H 5.13; N 9.17; S 6.43%.

IR spectrum (CH_2Cl_2): 3380(w), 1780(vs), 1710(vs), 1690(vs), 1600(w), 1510(m), 1490(m), 1230(m), cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 1.66 (s, $2CH_3$), 2.03 (s, $COCH_3$), 4.53 (s, OCH_2CO), 5.40—5.65 (m, C_5—H, C_6—H), 5.88 (s, C_3—H), 6.70—7.63 (m, $2C_6H_5$, CONH).

N-Phenyl-N-6-phenylacetamidopenicillanoyl acetamide (IV; R = $C_6H_5CH_2$, Z = $N(C_6H_5)$—CO—CH_3, n = O)

To a suspension of benzylpenicillin potassium (1.86 g, 5 mmol) in pyridine (0.4 g, 5 mmol) and methylene chloride (10 ml), cooled to 0 °C, a solution of *N*-chlorocarbonyl acetanilide (0.98 g, 5 mmol) in methylene chloride (10 ml) was added. The reaction mixture was stirred for 2 hours and worked up as in the previous case. A frothy residue was chromatographed over the silica gel column using the methylene chloride-ether gradient. The compound with R_f 0.50 was separated.

Yield: 1.58 g (70.5%); m. p. 82—5 °C; $[\alpha]_D^{23}$ + 185.1° (c 0.5, CH_2Cl_2); R_f 0.50 (System A).

Anal. $C_{24}H_{25}N_3O_4S$ (451.5), calc'd.: C 63.38; H 5.59; N 9.30%
found: C 63.52; H 5.82; N 9.57%.

IR spectrum (CH_2Cl_2): 3370(w), 1780(vs), 1705(vs), 1680(s,sh), 1490(m), 1370(m), 1233(s), 1173(w), 1075(w) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 1.47 and 1.58 (2s, $2CH_3$), 2.00 (s, $COCH_3$, 3.67 (s, $PhCH_2$), 5.32—5.65 (m, C_5—H, C_6—H), 5.80 (s, C_3—H), 6.23 (d, J = 10 Hz, CONH), 6.95—7.50 (m, $2C_6H_5$).

N-Propyl-N-6-phenylacetamidopenicillanoyl benzamide (IV; R = $C_6H_5CH_2$, Z = $N(C_3H_7)$—CO—C_6H_5, n = O)

To a suspension of benzypenicillin potassium (1.86 g, 5 mmol) in pyridine (0.4 g, 5 mmol) and toluene (20 ml), cooled to 0 °C, a solution of *N*-chlorocarbonyl-*N*-propyl benzamide (1.13 g, 5 mmol) in toluene (10 ml) was added. The reaction mixture was stirred for 1 hour at 0 °C, and water added (15 ml), stirred for 5 minutes, the organic layer separated, washed with water (15 ml) and dried ($MgSO_4$). After evaporation of the solvent, the residue was recrystallized from a mixture of toluene-petrolether.

Yield: 1.65 g (69%); m. p. 128—9 °C; $[\alpha]_D^{23}$ + 155.1° (c 0.5, CH_2Cl_2); R_f 0.61 (System A).

Anal. $C_{26}H_{29}N_3O_4S$ (479.5), calc'd.: C 65.12; H 6.10; N 8.76%
found: C 64.97; H 6.35; N 8.92%.

IR spectrum (KBr): 3340(m), 2960(m), 1775(s), 1675(vs), 1515(m,b), 1365(s), 1293(m), 1212(s), 1070(m), 725(m), 700(m) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): 0.80 (t, J = 8 Hz, CH_3), 1.15—1.75 (m, CH_2), 1.47 and 1.63 (2s, $2CH_3$), 3.20 and 4.20 (m, N—CH_2), 3.65 (s, $PhCH_2$), 5.13 (s, C_3—H), 5.40—5.70 (m, C_5—H, C_6—H), 6.27 (d, J = 9 Hz, CONH), 7.32 and 7.58 (2s, $2C_6H_5$).

Alcoholysis of Mixed Anhydrides

2,2,2-Trichloroethyl 6-Phenoxyacetamidopenicillanate 1-oxide (V; R = $C_6H_5OCH_2$, R′ = CCl_3CH_2, n = 1)

To a solution of phenoxyacetamidopenicillanic acid-1-oxide (0.66 g, 1.8 mmol) in pyridine (0.16 g, 2 mmol) and tetrahydrofurane (10 ml), a solution of *N*-chlorocarbonyl butyrolactam (0.29 g, 2 mmol) in tetrahydrofurane (5 ml) was added at —10 °C during a period of 15 minutes. Subsequently, 2,2,2-trichloroethanol (0.33 g, 2.2 mmol) was added and the reaction mixture stirred for 2 hours. The solvent was evaporated and the residue dissolved in methylene chlorid (20 ml) and water added (20 ml), stirred for 5 minutes, the organic layer separated and dried ($MgSO_4$). After evaporation of the solvent, the residue was crystallized by addition of ether.

Yield: 0.72 g (80%); m. p. 143—5 °C; IR and ^1H NMR spectra identical to data reported in lit.[12]

p-Nitrobenzyl 6-Phenylacetamidopenicillanate 1-oxide (V; $R = C_6H_5CH_2$, $R' = O_2NC_6H_5CH_2$, $n = 1$)

To a solution of phenylacetamidopenicillanic acid-1-oxide (0.63 g, 1.8 mmol) in pyridine (0.16 g, 2 mmol) and methylene chloride (10 ml), a solution of *N*-chlorocarbonyl butyrolactam (0.29 g, 2 mmol) in methylene chloride (5 ml) was added at 0 °C during a period of 10 minutes. After stirring the reaction mixture for 15 minutes, a solution of *p*-nitrobenzyl alcohol (0.34 g, 2.2 mmol) in methylene chloride (10 ml) was added and the reaction mixture stirred for 2 hours. Cold water (25 ml) was added, stirred for 5 minutes, the organic layer separated, washed with 1 M $NaHCO_3$ solution (10 ml), water (15 ml) and dried ($MgSO_4$). Evaporation of solvent gave a solid residue.

Yield: 0.74 g (85%); m. p. 140—2 °C; IR and ^1H NMR spectra identical to those reported in lit.[13]

Formation of Symmetric Anhydrides (IX)

7-Phenylacetamido-3-methyl-3-cephem-4-carboxylic anhidride (IX; $R = C_6H_5CH_2$)

a) 7-Phenylacetamido-3-methyl-3-cephem-4-carboxylic acid (0.33 g, 1 mmol) was dissolved in a solution of pyridine (0.18 g, 2.3 mmol) and methylene chloride (35 ml) with stirring, and *N*-chlorocarbonyl butyrolactam (0.2 g, 1.35 mmol) in methylene chloride (5 ml) added at 5 °C. The reaction solution was stirred for 2 hours. The precipitate was filtered and washed with methylene chloride.

Yield: 0.3 g (74%); m. p. 216—8 °C.

Anal. $C_{32}H_{30}N_4O_7S$ (646.75), calc'd.: C 59.43; H 4.67; N 8.66; S 9.92%
found: C 59.22; H 4.60; N 8.36; S 10.12%.

IR spectrum (KBr): 3280(s), 1790(s), 1765(vs), 1660(s), 1540(m), 1378(m), 1132(m), 1087(s), 1010(s), 725(w), 695(w) cm^{-1}.

^1H NMR spectrum (FX-90; DMSO-d_6): 2.18 (s, CH_3), 3.41 (s, $COCH_2Ph$), 3.20—4.01 (m, CH_2), 5.18 (d, $J = 4.5$ Hz, C_6—H), 5.66 (d, d, $J = 4.5$ and 8 Hz, C_7—H), 7.43 (s, C_6H_5), 9.3 (d, $J = 8$ Hz, CONH).

b) 7-Phenylacetamido-3-methyl-3-cephem-4-carboxylic acid (1.25 g, 3.8 mmol) was suspended in acetone (25 ml), pyridine (0.9 g, 8.9 mmol) and 2,2,2-trichloroethanol (0.62 g, 4.2 mmol) added, followed by a 20% solution of carbonyl dichloride in toluene (3 ml) at 0 °C, during a period of 30 minutes. The reaction mixture was stirred for additional 30 minutes, water (10 ml) added and the solvent decanted. The precipitate was suspended in ether, stirred, filtered and washed with ether.

Yield: 0.8 g (67%); m. p. 216—8 °C; IR and ^1H NMR spectra identical to those reported under a).

7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylic anhydride (IX; $R = C_6H_5OCH_2$)

7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid (3 g, 8.8 mmol) was dissolved in a solution of pyridine (0.79 g, 10 mmol) and 1,2-dichloroethane (50 ml) with stirring followed by *N*-chlorocarbonyl butyrolactam (1.5 g, 10 mmol) in 1,2-dichloroethane (15 ml). The reaction mixture was stirred at 0 °C for 5 hours. The separated crystalls were filtered and washed with cold 1,2-dichloroethane to give 1.31 g of the product. An additional quantity of the product was obtained by washing the mother liquor with water (2 × 10 ml); it was dried and the solvent evaporated. The residue was crystallized from acetone.

Yield: 1.89 g, (64%); m. p. 190—5 °C; R_f 0.86 (System B).

Anal. $C_{32}H_{30}N_4O_9S$ (678.75), calc'd.: C 56.62; H 4.45; N 8.25; S 9.45%
found: C 56.67; H 4.33; N 8.45; S 9.60%.

UV spectrum (dioxane, $c = 0.02$ mg/ml): λ_{max}: 269 nm ($\log \varepsilon = 3.1116$) and 276 nm ($\log \varepsilon = 3.1183$).

IR spectrum (KBr): 3250(s), 3037(w), 1780(sh), 1760(vs), 1672(s), 1530(m), 1470(m), 1365(s), 1210(s), 1072(s), 1000(m), 980(sh,m), 748(m), 680(m) cm^{-1}.

^1H NMR spectrum (FX-90; DMSO-d_6): 2.03 and 2.16 (2s, $2CH_3$), 3.40—3.70 (m, $2CH_2$), 4.62 (s, $2OCH_3$), 5.21—5.43 (m, $2C_6$—H), 5.70—6.02 (m, $2C_7$—H), 6.93—7.74 (m, $2C_6H_5$), 9.01—9.16 (m, 2NH).

b) According to the above procedure, 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid treated with *N*-chlorocarbonyl caprolactam gave 2.1 g (71%) of the product with the same m. p. The UV, IR and ^{1}H NMR spectra were identical to those reported under a).

c) 7-phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid (3.3 g, 9.5 mmol) was dissolved in a solution of pyridine (2.25 g, 28 mmol), acetone (30 ml) and 2,2,2-trichloroethanol (1.55 g, 10.5 mmol) was added, followed by a 20% solution of carbonyl dichloride in toluene (10 ml). The reaction mixture was stirred at 0 °C for 1 hour, water was added (25 ml) and the solution stirred for an additional hour. The separated crystalls were filtered, washed with acetone and dried.

Yield: 2.10 g (65%); m. p. 190—5 °C; R_f 0.86 (System B).

IR, UV and ^{1}H NMR spectra identical to those obtained under a).

From the mother liquor ,after evaporation of the solvent, 1.44 g (32%) of 2,2,2-trichloroethyl phenoxymethylcephalosporanate was obtained. M. p. and spectral data correspond to those reported in literature.[12]

Reactions of Symmetric Anhydrides (IX)

N-*Propyl-7-phenoxiacetamido-3-methyl-3-cephem-4-carboxamide* (*X*; $R = C_6H_5—OCH_2$, $R' = C_3H_7NH$)

To a solution of 7-Phenoxyacetomido-3-methyl-3-cephem-4-carboxylic anhydride (1 g, 1.5 mmol) in methylene chloride (50 ml) *n*-propylamine (0.09 g, 1.5 mmol) was added and the solution stirred at 40 °C for 1 hour. After crooling to 0 °C, water was added (20 ml) and *n*-propylamine to pH aprox. 9. The organic layer was separated, washed with water, dried ($MgSO_4$). After evaporation of the solvent, the residue was recrystallized from benzene.

Yield: 0.42 g (72%); m. p. 230—1 °C; R_f 0.57 (System A).

Anal. $C_{19}H_{23}N_3O_4S$ (389.48), calc'd.: C 58.59; H 5.95; N 10.79; S 8.23%
found: C 58.42; H 5.80; N 10.55; S 8.05%.

UV spectrum (dioxane, $c = 0.09$ mg/ml) λ_{max}: 265 nm ($\log \varepsilon = 2.8686$).

IR spectrum (KBr): 3260(s), 2942(m), 2910(m), 1757(vs), 1670(s), 1637(s), 1540(m), 1360(m), 1215(m), 1070(b,m), 745(m), 675(m) cm^{-1}.

^{1}H NMR spectrum (FX-90; DMSO-d_6): 0.86 (t, CH_3), 1.27—1.49 (m, CH_2), 1.96 (s, CH_3), 2.99—3.35 (m, N—CH_2, S—CH_2), 4.63 (s, OCH_2), 5.0 (d, $J = 4.8$ Hz, C_6—H), 5.46—5.61 (2d, $J = 4.8$ and 9.6 Hz, C_7—H), 6.79—7.69 (m, C_6H_5), 8.16 (m ,NH), 9.03 (d, $J = 8.5$ Hz, NH).

The water layer, after extraction, was acidified with dil. HCl (1 : 1) to pH aprox. 1 and extracted with methylene chloride (2 × 10 ml). Organic layer was dried and solvent evaporated.

Yield: 0.48 g (92%) of 7-Phenoxyacetamido-3-methyl-3-cephem-4-carboxylic acid.

2,2,2-Trichloroethyl phenoxymethylcephalosporanate (*X*; $R = C_6H_5OCH_2$, $R' = CCl_3CH_2O$)

To a solution of phenoxymethylcephalosporinic anhydride (0.34 g, 0.5 mmol) in methylene chloride (25 ml) 2,2,2-trichloroethanol (0.075 g, 0.5 mmol) was added with pyridine (0.01 g, 0.13 mmol) and the reaction solution stirred at 40 °C for 5 hours. To the cooled reaction solution, at 0 °C, water (10 ml) was added and dil. solution of HCl (1 : 1) to pH aprox. 2. The organic layer was separated, washed with water (2 × 5 ml), dried and the solvent evaporated. The residue was chromatographed over the silica gel column, using the methylene chloride-ether gradient. The compound with R_f 0.81 (System A) was separated.

Yield: 0.179 g (82.4%); m. p. 118—120 °C; IR and ^{1}H NMR spectra correspond to those reported in literature.[12]

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SAŽETAK

Mješoviti anhidridi penicilinske i cefalosporinske kiseline s *N*-acilkarbaminskom kiselinom

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Mješoviti anhidridi s penicilinskom kiselinom (*III*) nestabilni su i reagiraju dajući *N*-acilamide penicilinske kiseline (*IV*). Samo je anhidrid *III* s buturil laktamom dovoljno stabilan da alkoholizom daje estere penicilinske kiseline *V*. Mješoviti anhidridi s cefalosporinskom kiselinom (*VIII*) reagiraju dajući simetrične anhidride *IX*. Alkoholizom simetričnih anhidrida *IX* dobiveni su esteri cefalosporinske kiseline a aminolizom anhidrida *IX* dobiveni su amidi. Raspravlja se o mogućnosti nastajanja izomernoga mješovitog anhidrida s *O-imino esterom ugljične kiseline XIIIb*.