of (−)- or (+)-*cis*-3-methylfentanyl and such washing. The homogenate was then washed three times by centrifugation in 50 mM Tris·HCl, pH 7.4, and then assayed as described above with [$^3$H]DADL and [$^3$H]FOXY.

**(ii) With NG 108-15 Cell Membranes.** Membranes from NG108-15 neuroblastoma × glioma hybrid cells were used to assay binding of SUPERFIT analogues (by measuring competition with [$^3$H]DADL)[15] and their effects on adenylate cyclase[40] as described. Binding data were obtained in duplicate and adenylate cyclase determinations were in triplicate. Data were fitted to the Adair equation by using the program DATAPLOT developed by J. Filliben at the National Bureau of Standards.

(40) Sharma, S. K.; Nirenberg, M.; Klee, W. A. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 590.

**Registry No.** (−)-*cis*-**4**, 101472-20-2; (+)-*cis*-**4**, 101472-19-9; (−)-*trans*-**4**, 120143-77-3; (−)-*trans*-**4**·HCl, 120143-75-1; (+)-*trans*-**4**, 120143-78-4; (+)-*trans*-**4**·HCl, 120143-72-8; **5**, 31633-72-4; **6**, 120059-78-1; *cis*-**7**, 120059-79-2; *trans*-**7**, 120059-82-7; *cis*-**8**, 53757-54-3; *trans*-**8**, 57444-99-2; (+)-*trans*-**8**, 120143-73-9; (+)-*trans*-**8**·(+)-tartrate, 120199-48-6; (+)-*trans*-**8**·α-methylbenzylcarbamate, 120143-79-5; (+)-*trans*-**8**·2,4,6-trinitrobenzenesulfonic acid salt, 120143-76-2; (−)-*trans*-**8**, 120143-74-0; (−)-*trans*-**8**·(−)-tartrate, 120199-49-7; (−)-*trans*-**8**·α-methylbenzylcarbamate, 120143-80-8; (±)-*trans*-**8**·oxalate, 120059-83-8; (3*S*,4*S*)-*trans*-**9**, 120059-80-5; (3*R*,4*R*)-*trans*-**9**, 120059-84-9; (3*R*,4*R*)-*trans*-**10**, 120059-76-9; (3*R*,4*R*)-*trans*-**10**·HCl, 120059-85-0; (3*S*,4*S*)-*trans*-**10**, 120059-81-6; (3*S*,4*S*)-*trans*-**10**·HCl, 120085-47-4; (3*R*,4*R*)-*trans*-**11**·HCl, 120059-86-1; (3*S*,4*S*)-*trans*-**11**·HCl, 120059-77-0; adenylate cyclase, 9012-42-4; aniline, 62-53-3; (*R*)-(+)-α-methylbenzylisocyanate, 33375-06-3; 4-nitrophenethyl bromide, 5339-26-4.

# Synthesis and Antimicrobial Properties of Substituted β-Aminoxypropionyl Penicillins and Cephalosporins[1]

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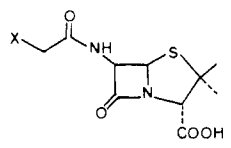
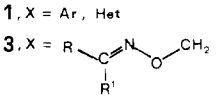
Some β-aminoxypropionyl penicillins (**3**) and cephalosporins (**4** and **5**), planned on the basis of the hypothesis that the (methyleneaminoxy)methyl group (>C=NOCH$_2$) could be a "bioisoster" of either aryls or other aromatic groups, were synthesized and assayed for their antimicrobial properties. Compounds **3–5**, tested on Gram-positive and Gram-negative bacteria, both sensitive to enzyme inactivation and otherwise, exhibited an activity trend that was not substantially different from that of the corresponding phenylacetamido derivatives taken as terms of comparison.

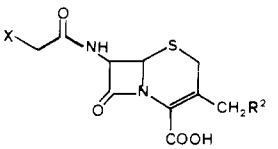
It is usually recognized that the changes on the side chain linked to the β-lactam nucleus of β-lactam antibiotics exert an influence that is sometimes decisive on the potency and range of the antimicrobial activity spectrum, stability to acids, and resistance to enzyme inactivation.[2] The numerous studies that have been carried out on the structure–activity relationships of these antibiotics have not yet made it possible to establish a precise correlation between the nature of these side chains and antimicrobial activity.[3] However, it may be pointed out that, in general, in the field of the more classic β-lactam antibiotics such as penicillins and cephalosporins, such compounds widely used in therapeutic practice such as penicillin G, ampicillin, cefalexin, and cefamandole present side chains of an acetamido type, substituted by an aryl or by an aromatic heterocycle, as shown in **1** and **2**, linked to the β-lactam nucleus.



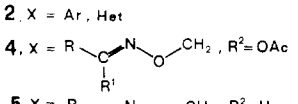
**1**, X = Ar, Het



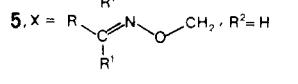
**3**, X = R, R$^1$, CH$_2$



**2**, X = Ar, Het



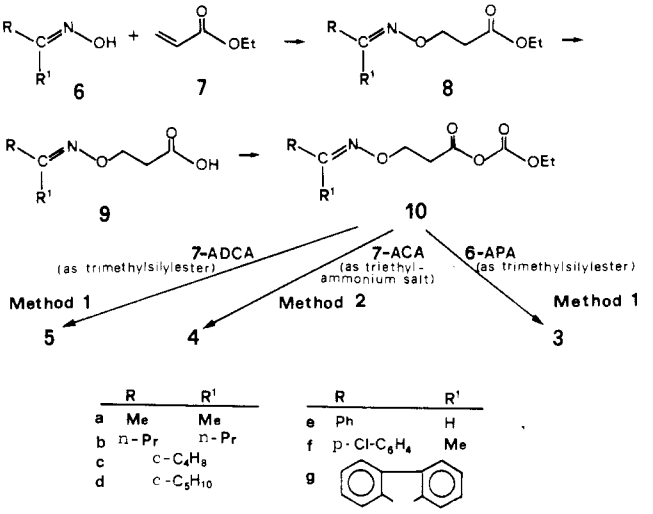
**4**, X = R, R$^1$, CH$_2$, R$^2$ = OAc



**5**, X = R, R$^1$, CH$_2$, R$^2$ = H

The results of both experimental and theoretical studies[4] carried out on the mechanism of drug–receptor interactions in the field of adrenergic drugs indicated that a suitable

**Scheme I**




nonaromatic moiety, such as the (methyleneaminoxy)methyl group (>C=NOCH$_2$) could be a "bioisoster"[5] of

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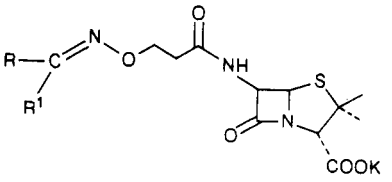
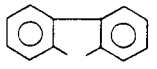
‡ ISF-Laboratori per la Ricerca Biomedica.
§ Present address: Lab. BT, 21047 Saronno, Varese, Italy.
⊥ Istituto di Chimica Organica.

(1) A preliminary account of this work was presented at the 15th National Meeting of the Italian Chemical Society, Grado, September 1984, Abstr, p 140.
(2) (a) Price, K. E. *Structure Activity Relationships Among the Semisynthetic Antibiotics*; Academic Press: New York, 1977; pp 1, 61. (b) Sassiver, M. L.; Lewis, A. ref 2a; p 87. (c) Webber, J. A.; Wheeler, W. J. *Chemistry and Biology of β-Lactam Antibiotics*; Academic Press: New York, 1982; p 371. (d) Boyd, D. B. ref 2c; p 437.
(3) See for example: (a) Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Giani, R.; Pinza, M.; Broccali, G. *J. Med. Chem.* **1983**, *26*, 1648 and references therein cited. (b) Cimarusti, C. M. *J. Med. Chem.* **1984**, *27*, 247.
(4) Macchia, B.; Balsamo, A.; Lapucci, A.; Martinelli, A.; Macchia, F.; Breschi, M. C.; Fantoni, B.; Martinotti, E. *J. Med. Chem.* **1985**, *28*, 153 and references therein cited.

0022-2623/89/1832-1398$01.50/0 

**Table I.** β-Aminoxypropionyl Penicillin Derivatives



| compd | R | $R^1$ | recrystn solvent[a] | method | yield,[b] % | formula[c] | $^1H$ NMR, δ |
|---|---|---|---|---|---|---|---|
| **3c** | c-$C_4H_8$ | | A | 1 | 24 | $C_{16}H_{22}N_3O_5SK$ | ($D_2O$) 1.52 [s, 6, $SC(CH_3)_2$], 5.54 (m, 2, NHC*H* and CHS) |
| **3d** | c-$C_5H_{10}$ | | B | 1 | 30 | $C_{17}H_{24}N_3O_5SK$ | ($D_2O$) 1.51 [s, 6, $SC(CH_3)_2$], 5.54 (m, 2, NHC*H* and CHS) |
| **3e** | Ph | H | A | 1 | 40 | $C_{18}H_{20}N_3O_5SK$ | ($D_2O$) 1.48 and 1.53 [2s, 6, $SC(CH_3)_2$], 4.23 (s, 1, CHCOO), 5.57 (m, 2, NHC*H* and CHS), 8.10 (s, 1, PhC*H*) |
| **3g** |  | | B | 1 | 35 | $C_{24}H_{22}N_3O_5SK$ | ($D_2O$–$Me_2SO$-$d_6$) 1.33 [s, 6, $SC(CH_3)_2$], 5.47 (m, 2, NHC*H* and CHS) |

[a] A = EtOH–$Et_2O$; B = MeOH; C = MeOH–$Et_2O$. [b] No efforts were made to optimize yields. [c] Anal. C, H, N.

either aryls or other aromatic groups.[4] These results suggested that it might be possible to effect the substitution of an aryl with an aminoxymethyl group in drugs different from adrenergics. This has been proven to be effective in the case of arylacetic antiinflammatory agents.[6]

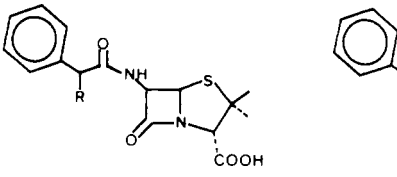
On the basis of these considerations, it appeared to be of interest to test this substitution also in the field of penicillins and cephalosporins of types **1** and **2**, respectively. We thus planned the synthesis and the evaluation of the antimicrobial properties of β-aminoxypropionyl-APAs (**3**), -ACAs (**4**), and -ADCAs (**5**), which can be viewed as analogues of arylacetyl-APAs (**1**), -ACAs (**2**, $R^2$ = OAc), and -ADCAs (**2**, $R^2$ = H), respectively, in which the Ar portion has been substituted by an aminoxymethyl moiety. The substituents (whether aliphatic or aromatic) on the aminoxy moiety of the new penicillins (**3**) and cephalosporins (**4** and **5**) (see Scheme I) were chosen in such a way as to obtain compounds exhibiting the widest range of electronic, steric, and lipophilic characteristics.

## Chemistry

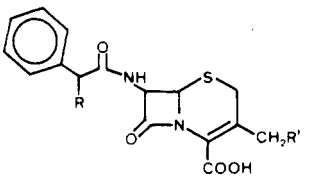
The synthetic route to the penicillins **3** (Table I) and the cephalosporins **4** and **5** (Table II) is described in Scheme I. The intermediate β-aminoxypropionic acids **9** were prepared, as previously reported,[6] by Michael-type reaction of the oximes **6** with ethyl acrylate (**7**) and subsequent alkaline hydrolysis of the corresponding ethyl ester **8**. The acids **9**, activated as mixed anhydrides (**10**), were transformed into **3**–**5** in accordance with method 1 or 2 (Scheme I). Method 1 involves the reaction of the mixed anhydride **10**, prepared by reaction of the appropriate acid **9** with ethyl chloroformate and 6β-amino-2,2-dimethylpenam-3α-carboxylic acid (6-APA) or 7β-amino-3-methyl-3-cephem-4-carboxylic acid (7-ADCA), protected as trimethylsilyl esters, followed by mild hydrolysis to the free acids **3** and **5**. Method 2 consists of the reaction of the anhydride **10** with the triethylammonium salt of 7β-amino-3-(acetoxymethyl)-3-cephem-4-carboxylic acid (7-ACA), which directly affords the acids **4**.

## Results and Discussion

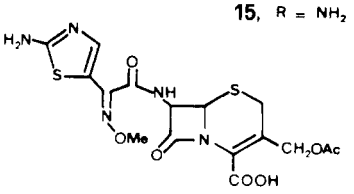
Table III shows the antimicrobial activity of the new penicillins (**3**) and cephalosporins (**4** and **5**), expressed as the geometrical average of the minimum inhibitory concentrations (MICs), toward Gram-positive and Gram-negative bacteria, which may or may not produce β-lactamases. Table III also shows the antimicrobial activity of 6-(phenylacetamido)penicillanic acid (**11**, penicillin G), 7-(phenylacetamido)cephalosporanic acid (**13**, cephaloram), and 7-(phenylacetamido)desacetoxycephalosporanic acid (**14**), taken for comparison. The choice, as reference compounds, of β-lactam derivatives not substituted on the aromatic ring was made on the basis of indications in literature that the introduction of substituents on the aromatic ring of phenylacetamido penicillin and cephalosporin derivatives has little or no influence on their activity.[2a,b] Table III furthermore shows the antimicrobial activity of clinically important penicillins and cephalosporins of types **1** and **2**, respectively, such as ampicillin (**12**), cefotaxime (**16**), and cephalexin (**15**).



**11**, R = H
**12**, R = $NH_2$



**13**, R = H, R' = OAc
**14**, R = H, R' = H
**15**, R = $NH_2$, R' = H

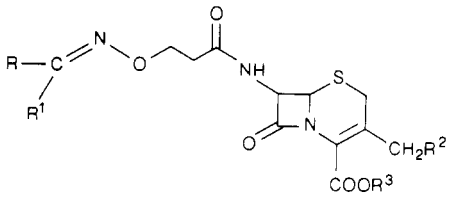


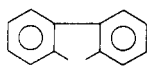
**16**

An examination of the MIC values listed in Table III indicates that the activity trend of the aminoxy ethereal compounds **3**–**5** toward the various kinds of microorganisms tested is not substantially different from that of the corresponding phenylacetamido derivatives taken as reference compounds, i.e. penicillin G (**11**), cephaloram (**13**), and 7-(phenylacetamido)desacetoxycephalosporanic acid (**14**), respectively. These results would thus appear to be in agreement with the hypothesis that the aminoxymethyl moiety may be able to substitute a phenyl more or less substituted also in classes of drugs different from those of adrenergic and nonsteroidal antiinflammatory drugs. An examination of the microbiological data also reveals that the activity of the new aminoxy ethereal penicillin (**3**) and cephalosporin (**4** and **5**) derivatives toward Gram-positive bacteria, whether sensitive or resistant to enzime inactivation, is comparable and at times superior to that

(5) (a) Burger, A. *A Guide to the Chemical Basis of the Drug Design*; Wiley-Interscience: New York, 1983; pp 28, 84. (b) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563.
(6) Balsamo, A.; Macchia, B.; Macchia, F.; Orlandini, E.; Domiano, P.; Baldacci, M.; Volpato, I. Joint Meeting on Medicinal Chemistry, Rimini, May 1985, Abstr. T12.

**Table II.** β-Aminoxypropionyl Cephalosporin Derivatives



| compd | R | $R^1$ | $R^2$ | $R^3$ | mp, °C | method | recrystn solvent[a] | yield,[b] % | formula[c] | $^1$H NMR, δ |
|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | Me | Me | OAc | H | 120–123 | 2 | A | 35 | $C_{16}H_{21}N_3O_7S$ | ($CDCl_3$) 1.80 [s, 6, $(CH_3)_2C$], 2.03 (s, 3, $CH_3CO$), 3.30 and 3.65 (2 d, 2, $J$ = 17.6 Hz, $SCH_2$), 4.98 (d, 1, $J$ = 4.6 Hz, CHS), 5.66 (q, 1, $J$ = 4.6 and 8.4 Hz, NHC*H*) |
| **4b** | *n*-Pr | *n*-Pr | OAc | H | 146–147 | 2 | B | 22 | $C_{20}H_{29}N_3O_7S$ | ($Me_2SO$-$d_6$) 2.03 (s, 3, $CH_3CO$), 3.32 and 3.69 (2 d, 2, $J$ = 4.8 Hz, CHS), 5.67 (q, 1, $J$ = 4.8 and 8.4 Hz, NHC*H*) |
| **4c** | c-$C_4H_8$ | | OAc | H | 145 dec | 2 | B | 28 | $C_{18}H_{23}N_3O_7S$ | ($Me_2SO$-$d_6$) 2.10 (s, 3, $CH_3CO$), 3.27 and 3.63 (2 d, 2, $J$ = 19.0 Hz, $SCH_2$), 5.80 (q, 1, $J$ = 4.0 and 8.4 Hz, NHC*H*) |
| **4d** | c-$C_5H_{10}$ | | OAc | H | 158–160 | 2 | A | 24 | $C_{19}H_{25}N_3O_7S$ | ($Me_2SO$-$d_6$) 2.05 (s, 3, $CH_3CO$), 3.27 and 3.63 (2 d, 2, $J$ = 18.0 Hz, $SCH_2$), 4.97 (d, 1, $J$ = 4.8 and 8.4 Hz, NHC*H*) |
| **4e** | Ph | H | OAc | H | 143–145 | 2 | B | 37 | $C_{20}H_{21}N_3O_7S$ | ($CDCl_3$) 2.07 (s, 3, $CH_3CO$), 3.22 and 3.60 (2 d, 2, $J$ = 18.0 Hz, $SCH_2$), 5.00 (d, 1, $J$ = 4.8 Hz, NHC*H*), 9.35 (s, 1, PhC*H*) |
| **4f** | *p*-Cl-$C_6H_4$ | Me | OAc | K | | 2 | C | 25 | $C_{21}H_{21}ClN_3O_7SK$ | ($D_2O$) 2.05 (s, 3, $CH_3CO$), 3.40 (s, 3, $CH_3CN$), 5.73 (d, 1, $J$ = 4.4 Hz, NHC*H*) |
| **4g** |  | | OAc | H | 180–181 | 2 | A | 21 | $C_{26}H_{23}N_3O_7S$ | ($Me_2SO$-$d_6$) 2.06 (s, 3, $CH_3CO$), 5.75 (q, 1, $J$ = 4.8 and 8.0 Hz, NHC*H*) |
| **5b** | *n*-Pr | *n*-Pr | H | H | 67–68 | 1 | B | 25 | $C_{18}H_{27}N_3O_5S$ | ($CDCl_3$–$Me_2SO$-$d_6$) 2.15 (s, 3, $CH_3C$), 3.13 and 3.58 (2 d, 2, $J$ = 17.6 Hz, $SCH_2$), 5.00 (d, 1, $J$ = 4.8 Hz, CHS), 5.93 (q, 1, $J$ = 4.8 and 8.6 Hz, NHC*H*) |
| **5c** | c-$C_4H_8$ | | H | H | 168–170 | 1 | A | 21 | $C_{16}H_{21}N_3O_5S$ | ($CDCl_3$) 2.16 (s, 3, $CH_3$), 3.14 and 3.60 (2 d, 2, $J$ = 18.8 Hz, $SCH_2$), 4.99 (d, 1, $J$ = 4.6 Hz, CHS), 5.77 (q, 1, $J$ = 4.6 and 8.0 Hz, NHC*H*) |
| **5d** | c-$C_5H_{10}$ | | H | H | 143–145 | 1 | D | 32 | $C_{17}H_{23}N_3O_5S$ | ($CDCl_3$) 2.13 (s, 3, $CH_3$), 4.99 (d, 1, $J$ = 4.8 Hz, CHS), 5.67 (q, 1, $J$ = 8.0 Hz, NHC*H*) |
| **5e** | Ph | H | H | H | 89–90 | 1 | A | 33 | $C_{18}H_{19}N_3O_5S$ | ($CDCl_3$–$Me_2SO$-$d_6$) 2.10 (s, 3, $CH_3$), 3.11 and 3.50 (2 d, 2, $J$ = 18.0 Hz, $SCH_3$), 4.97 (d, 1, $J$ = 4.8 Hz, CHS), 5.73 (q, 1, $J$ = 4.8 and 8.4 Hz, NHC*H*), 8.11 (s, 1, PhC*H*) |
| **5f** | *p*-Cl-$C_6H_4$ | Me | H | H | 86–87 | 1 | A | 39 | $C_{19}H_{20}N_3O_5S$ | ($CDCl_3$–$Me_2SO$-$d_6$) 2.13 (s, 3, $CH_3$), 2.20 (s, 3, $CH_3CN$), 3.12 and 3.53 (2 d, 2, $J$ = 18.0 Hz, $SCH_2$), 5.77 (q, 1, $J$ = 4.4 and 8.6 Hz, NHC*H*) |

[a] A = AcOEt; B = AcOEt–petroleum ether; C = MeOH; D = *i*-PrOH–*i*-$Pr_2O$. [b] No efforts were made to optimize yields. [c] Anal. C, H, N.

of ampicillin (**12**), cefotaxime (**16**), and cephalexin (**15**), respectively. This is particularly noticeable in the case of the (9-fluorenylideneaminoxy)propionyl derivative of 7-ACA (**4g**), which toward these organisms proves to be 10 and 25 times, respectively, more active than cefotaxime (**16**). However, the comparison of the activity against Gram-negative germs of the new aminoxy ethereal antibiotics (**3–5**) with that of the clinically important antibiotics **12**, **15**, and **16** is decidedly favorable to the latter. It may be noted that the above-mentioned antibiotics, **12**, **15**, and **16**, exhibit arylacetamido side chains that are further substituted by an amino group, in the case of ampicillin (**12**) and cephalexin (**15**), and the methoxyimino group, in the case of cefotaxime (**16**). These substituents are usually reported to be important in increasing the antibiotic properties, especially toward Gram-negative bacteria.[2a,b,3b]

## Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra for comparison of compounds were taken as paraffin oil mulls or as liquid films on a Perkin-Elmer Model 1310 instrument. $^1$H NMR spectra were obtained in ca. 10% $CDCl_3$ [for the free acids ($Me_4Si$)] and $D_2O$ or $Me_2SO$-$d_6$ [for salts ($Me_3SiCD_2CD_2COONa$)] solutions with a Varian EM 360 A spectrometer. The proton magnetic resonance assignments were established on the basis of the expected chemical shifts and the multiplicity of the signals. Evaporations were made in vacuo (rotating evaporator). $MgSO_4$ was always used as a drying agent. Tetrahydrofuran (THF), $CHCl_3$, triethylamine, and dioxane were refluxed over $LiAlH_4$, $P_2O_5$, phenyl isocyanate, and Na, respectively, and then rectified. Dimethylformamide (DMF) was passed through an aluminum oxide (activity I) column, degassed with $N_2$, and dried on molecular sieves. Petroleum ether refers to the fraction boiling at 60–80 °C. Elemental analyses were performed in our analytical laboratory and agreed with the theoretical values to within ±0.4%.

**3-Aminoxypropionic Acid Derivatives 9a–g.**[6] A solution of the appropriate oxime (**6a–g**) (0.5 mol) in anhydrous EtOH (250 mL) was treated with ethyl acrylate (**7**) (0.42 mol) and then with a solution of 2 N KOH in anhydrous EtOH (42 mL). The resulting mixture was stirred at 35 °C for 48 h and then evaporated. The solid residue was dissolved in $Et_2O$, washed (aqueous 10% NaOH and $H_2O$), dried, filtered, and evaporated to dryness to yield the crude ester **8**, which was purified by distillation (**8a–f**) or by crystallization (**8g**). [**8a** (40%): bp 66–70 °C (1.5 mm). Anal. ($C_8H_{15}NO_3$) C, H, N. **8b** (48%): bp 75–78 °C (2.0 mm). Anal. ($C_{12}H_{23}NO_3$) C, H, N. **8c** (38%): bp 102–105 °C (1.5 mm). Anal. ($C_{10}H_{17}NO_3$) C, H, N. **8d** (41%): 120–124 °C (1.2 mm). Anal. ($C_{11}H_{19}NO_3$) C, H, N. **8e** (45%): bp 79–80 °C (0.5 mm). Anal. ($C_{12}H_{15}NO_3$) C, H, N. **8f** (70%): bp 102–106 °C (0.3 mm). Anal. ($C_{13}H_{16}ClNO_3$) C, H, N. **8g** (30%): mp 198–200 °C ($CHCl_3$–hexane). Anal. ($C_{18}H_{17}NO_3$) C, H, N.]

Each of the esters **8** (0.05 mol) was added to a solution of KOH (0.06 mol) in EtOH (30 mL). After 48 h at room temperature, the solvent was evaporated and the residue was taken up with

**Table III.** Antibacterial Activity of Penicillin (3) and Cephalosporin (4, 5) Derivatives

| compd | MIC,[a] μg/mL | | | |
|---|---|---|---|---|
| | Gram-positive[b] | Gram-positive resistant[c] | Gram-negative[d] | Gram-negative resistant[e] |
| **3c** | 0.06 | 25 | 53 | >200 |
| **3d** | 0.20 | 25 | 107 | >200 |
| **3e** | 0.10 | 50 | 136 | >200 |
| **3g** | 0.06 | 8.0 | 131 | >200 |
| 11 (penicillin G) | 0.05 | 79 | 71 | >200 |
| 12 (ampicillin) | 0.04 | 10 | 1.0 | >200 |
| **4a** | 1.70 | 6.2 | 174 | >200 |
| **4b** | 0.73 | 10 | 93 | >200 |
| **4c** | 0.59 | 7.3 | 71 | >200 |
| **4d** | 0.50 | 1.9 | 174 | >200 |
| **4e** | 0.22 | 4.0 | 71 | >200 |
| **4f** | 0.25 | 4.0 | 151 | >200 |
| **4g** | 0.02 | 0.25 | 44 | >100 |
| 13 (cephaloram) | 1.06 | 12.6 | 29 | >200 |
| 16 (cefotaxime) | 0.22 | 6.2 | 0.02 | 0.1 |
| **5b** | 16.4 | 100 | >200 | >200 |
| **5c** | 9.1 | 79 | 131 | >200 |
| **5d** | 7.3 | 79 | 131 | >200 |
| **5e** | 8.2 | 79 | >200 | >200 |
| **5f** | 4.7 | 63 | >200 | >200 |
| 14 ((phenylacetamido)desacetoxycephalosporanic acid) | 6.2 | 200 | 123 | >200 |
| 15 (cephalexin) | 0.4 | 20 | 2.0 | >100 |

[a] The in vitro antibacterial activities were evaluated by the 2-fold serial agar dilution method with a multiinocular device (see ref 7). Results are reported as geometrical averages of MICs. [b] Strains tested: *S. aureus* Smith, *S. aureus* 9144, *S. aureus* 6538/P, *S. pyogenes* ISM 68/231, *S. pyogenes* ISM 68/241, *S. pyogenes* β-haem. A, *S. pneumoniae* Felton, *S. faecalis* ATCC 6057, *S. lutea* ATCC 9341. [c] Strains tested: *S. aureus* F.2, *S. aureus* 6014668, *S. aureus* 39/II FBF. [d] Strains tested: *E. coli* 120, *S. typhi* 6/12, *S. typhimurium* No, *S. enteritidis* To, *S. paratyphi* B To, *S. dysenteriae* NCTC 4837, *N. meningitidis* To, *K. pneumoniae* ATCC 10031, *P. providence* To, *P. mirabilis* OSCB 2. [e] Strains tested: *E. coli* R+ TEM, *E. cloacae* 214, *A. cloacae* 653, *P. aeruginosa* ISF 1.

$H_2O$. The aqueous phase was washed with $Et_2O$, acidified to pH 4–5 with 10% aqueous HCl, and extracted with $Et_2O$. Evaporation of the washed ($H_2O$) and filtered extracts gave the crude acid **9**, which was purified by distillation (**9a,b**) or by crystallization from the proper solvent (**9c–g**). [**9a** (70%): bp 104–105 °C (4.0 mm). Anal. ($C_6H_{11}NO_3$) C, H, N. **9b** (81%): bp 121–123 °C (0.3 mm). Anal. ($C_{10}H_{19}NO_3$) C, H, N. **9c** (72%): mp 60–62 °C (petroleum ether). Anal. ($C_8H_{13}NO_3$) C, H, N. **9d** (73%) mp 38–39 °C (petroleum ether). Anal. ($C_9H_{15}NO_3$) C, H, N. **9e** (84%): mp 66–68 °C (hexane). Anal. ($C_{10}H_{11}NO_3$). **9f** (80%): mp 83–85 °C (hexane) (lit.[8] mp 80–83 °C). **9g** (68%): mp 127–129 °C ($CHCl_3$–petroleum ether). Anal. ($C_{16}H_{13}NO_3$) C, H, N.]

**General Procedure for the Preparation of 6β-(3-Aminoxypropionamido)-2,2-dimethylpenam-3α-carboxylic Acid (3c–e,g) and 7β-(3-Aminoxypropionamido)-3-methyl-3-cephem-4-carboxylic Acid (5b–f) Derivatives. Method 1.** A solution of the appropriate acid **9**[6] (5.4 mmol) and $Et_3N$ (5.2 mmol) in anhydrous 1:1 $CHCl_3$–dioxane mixture (10 mL) was treated at −10 °C with stirring with a solution of ClCOOEt (5.4 mmol) in the same solvent mixture (10 mL). After 30 min at −10 °C, the stirred suspension was treated dropwise at room temperature with a solution of the trimethylsilyl ester of the 6-APA or 7-ADCA [prepared by refluxing a suspension of 6-APA or 7-ADCA (6.3 mmol) and hexamethyldisilazane (11.8 mmol) in anhydrous $CHCl_3$ (12 mL)] in anhydrous dioxane (12 mL). The resulting mixture was stirred at room temperature for 45 min and at 36 °C for 15 min, filtered, and treated with a 1:1 EtOH–$H_2O$ mixture (1.6 mL). After 10 min at the same temperature, the mixture was filtered, acidified with 20% $H_3PO_4$ to pH 2.8, and then extracted with AcOEt. Evaporation of the washed ($H_2O$) organic extracts gave a residue which in the case of 7-ADCA derivatives was triturated with a 1:3 mixture of $Et_2O$–petroleum ether to yield crude **5** as a solid product, which was purified by crystallization from the proper solvent (see Table II); in the case of the 6-APA derivatives, the crude product was dissolved in anhydrous EtOH and treated with a stoichiometric amount of anhydrous AcOK. The precipitate was filtered and crystallized from the proper solvent to yield **3** as potassium salt (see Table I).

**General Procedure for the Synthesis of 7β-(3-Aminoxypropionamido)-3-(acetoxymethyl)-3-cephem-4-carboxylic Acid Derivatives (4a–g). Method 2.** A stirred solution of the appropriate acid **9** (6.4 mmol) and $Et_3N$ (6.3 mmol) in anhydrous THF (15 mL) was treated dropwise at −10 °C with a solution of ClCOOEt (6.4 mmol) in anhydrous THF (5 mL). After 30 min at the same temperature, the resulting suspension was added dropwise with stirring to a cooled (0 °C) suspension of 7-ACA (6.2 mmol) and $Et_3N$ (6.3 mmol) in anhydrous DMF (10 mL). The mixture was stirred at 0 °C for 1 h and at 20 °C for 15 min, filtered, concentrated at reduced pressure, diluted with $H_2O$, and washed with AcOEt. The aqueous phase was acidified with 10% aqueous HCl to pH 2.8 and extracted with AcOEt. Evaporation of the washed ($H_2O$) organic extracts gave an oily residue, which was triturated with a 1:3 mixture of $Et_2O$–petroleum ether to yield practically pure **4**, which was crystallized from the proper solvent (**4a–e,g**) or transformed into the potassium salt (**4f**) (see Table II).

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**Registry No.** **3c** acid, 119881-38-8; **3c** potassium salt, 119881-33-3; **3d** acid, 119881-39-9; **3d** potassium salt, 119881-34-4; **3e** acid, 119881-41-3; **3e** potassium salt, 119881-35-5; **3g** acid, 119881-40-2; **3g** potassium salt, 119881-36-6; **4a**, 119881-21-9; **4b**, 119881-22-0; **4c**, 119881-23-1; **4d**, 119881-24-2; **4e**, 119881-25-3; **4f** acid, 119881-37-7; **4f** potassium salt, 119881-26-4; **4g**, 119881-27-5; **5b**, 119881-28-6; **5c**, 119881-29-7; **5d**, 119881-30-0; **5e**, 119881-31-1; **5f**, 119881-32-2; **6a**, 127-06-0; **6b**, 1188-63-2; **6c**, 1192-28-5; **6d**, 100-64-1; **6e**, 932-90-1; **6f**, 1956-39-4; **6g**, 2157-52-0; **7**, 140-88-5; **8a**, 119881-14-0; **8b**, 119881-15-1; **8c**, 119881-16-2; **8d**, 119881-17-3; **8e**, 119881-18-4; **8f**, 28191-82-4; **8g**, 119881-19-5; **9a**, 103586-55-6; **9b**, 103586-56-7; **9c**, 103586-53-4; **9d**, 103586-54-5; **9e**, 119881-20-8; **9f**, 63506-82-1; **9g**, 103586-60-3; 6-APA $Me_3Si$ ester, 1025-55-4; 7-ADCA $Me_3Si$ ester, 41360-37-6; 7-ACA, 957-68-6.

**Supplementary Material Available:** Tables showing the MIC values of the penicillins **3** and the cephalosporins **4** and **5** toward the individual Gram-positive and Gram-negative microorganisms tested (Tables IV and V, respectively) (2 pages). Ordering information is given on any current masthead page.

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