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SYNTHESIS OF 2-OXOCEPHALOSPORINS

DAIJIRO HAGIWARA, MATSUHIKO ARATANI, KEIJI HEMMI and MASASHI HASHIMOTO*
Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. 2-1-6, Kashima, Yodogawa-ku, Osaka 532

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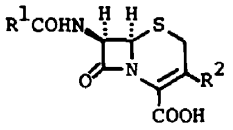
Abstract—A synthesis of the 2-oxocephalosporin nucleus (**12**) has been achieved starting from penicillin V. Some physical and chemical properties of this new ring system and the preparation of the corresponding free acid **2** ($R^1=CH_2OC_6H_5$) for biological testing are also described.

In the β-lactam antibiotic field, recent efforts have been increasingly focused on the synthesis of new bicyclic ring structures. As part of our continuing program in this area, we have been engaged in altering the dihydrothiazine ring of the cephalosporin nucleus (**1**) with a view to obtaining unique cephalosporin antibiotics.[1] In view of the supposed correlation between the biological activity and the chemical reactivity of the β-lactam antibiotics,[2] we have had an interest in preparing cephalosporin derivatives containing more reactive β-lactam ring systems. The synthesis of 2-oxocephalosporins (**2**) on which we describe here has been undertaken based on the anticipation that the introduction of the 2-oxo group on the cephalosporin nucleus would enhance the reactivity of its β-lactam carbonyl via a vinylogous amide resonance by a delocalization of the unshared electron pair of the β-lactam nitrogen into the adjacent α,β-unsaturated carbonyl system. After the completion of this series of work,[3] there have appeared three reports on the synthesis of the 2-oxocephalosporin derivatives by Kim *et al*,[4] Rosati *et al*,[5] and Ernest,[6] respectively. This prompts us to report our own work on the synthesis of 2-oxocephalosporins by a different chemical approach.

Our starting material was the 4-mercapto-azetidinone **3** which had been prepared from penicillin V by Baldwin *et al.*[7] Acylation of the mercapto group of **3** with trichloroethoxycarbonyloxyacetyl chloride[8] gave the thiolate **4** in quantitative yield. Preliminary attempts to effect the isomerization of the β,γ-unsaturated ester function of **4** into the conjugated ester using organic bases gave complex product mixtures, from which the desired product **5** was at the best isolated only in 30% yield, although the subsequent ozonolysis of **5** provided a fairly good result, giving the crystalline oxalyl derivative **6**.

It was thought that the unsatisfactory result in the above isomerization was probably due to the susceptibility of the thioester group of **4** to the base treatments, and accordingly it was decided to seek another route to **6**. For this purpose, the thiolate **4** was ozonized first of all to give the β-keto ester **7** in quantitative yield. We surmised that this keto ester would exist rather completely in the enolate form and have tendency further to consume ozone and to give the desired oxalyl derivative **6**. Indeed, when **7** was ozonized in AcOEt at low temperature as usual, the reaction proceeded smoothly to give **6** in 60% yield based on **4**.

The next step in our synthesis was the conversion of this intermediate **6** into the phosphorane **10**.[9] For this purpose, we first examined the reduction of **6** to the carbinolamide **8** and, after several attempts, this was



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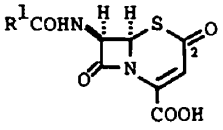

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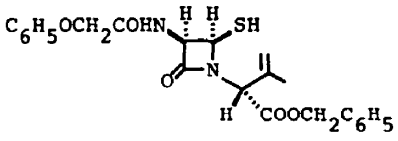

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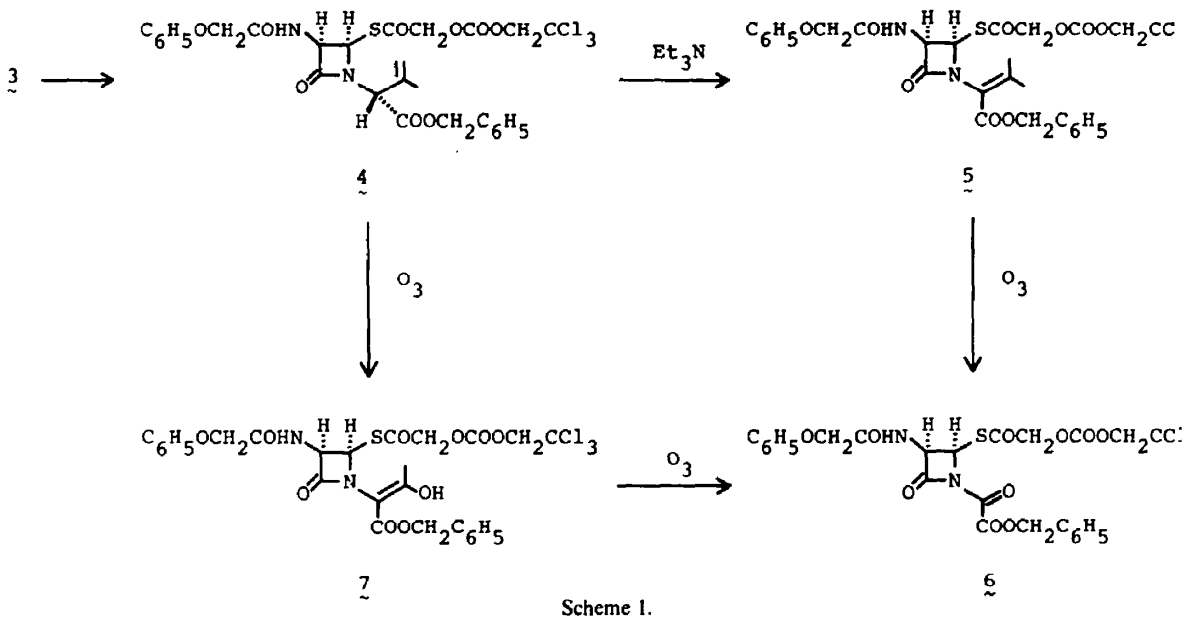


Scheme 1.

achieved by using Al-Hg in wet THF. The carbinolamide **8** so obtained as a 1:1 mixture of the diastereoisomers was used in the next reaction without purification. Thus, **8** was chlorinated with $SOCl_2$ in the presence of 2,6-lutidine in CH_2Cl_2 and subsequently reacted with triphenylphosphine in the same solvent to give the phosphorane **10** in 40% yield from **6** after purification by silica gel chromatography.

For construction of the 2-oxocephem nucleus from this phosphorane **10**, the trichloroethoxycarbonyl protective group was then removed by reduction with Zn dust in the presence of AcOH in CH_2Cl_2 to give the alcohol **11**, which was finally subjected to oxidation using DMSO in combination with Ac_2O, yielding the 2-oxocephem **12**, via a spontaneous cyclization of the resulting aldehyde, in 65% yield from **10**.

The 2-oxocephem structure was characterized by the following spectral and chemical properties. A very characteristic signal in the NMR spectrum of **12** is that of the C-6 proton which appeared at a considerably lower field (δ 6.05 in DMSO-d_6), as compared with the normal cephalosporins whose corresponding protons resonated at δ 4.24 ~ 5.46.[10] The 2-oxocephem spectrum was further characterized by a singlet signal originating from H-3 at δ 6.33. In the UV spectrum (dioxane), **12** displayed a long wavelength maximum at 314 nm (ε, 6000), reflecting the conjugation of the 2-oxo group to the C-3 double bond. The IR spectrum of **12** showed a very high wavenumber absorption of the β-lactam carbonyl group at 1805 cm^{-1}, thus suggesting a highly reactive β-lactam ring system in **12**.

In fact, **12** was found to be quite labile under basic conditions. For instance, when left in MeOH containing a trace of pyridine, **12** was almost completely decomposed after 2.5 hr to the non-β-lactam compounds **13** and **14**, separable by chromatography. Examination by tlc showed the initial formation of **13** which was then converted into **14** slowly. These compounds were found to be optically active and interconversible in polar solvents. An examination by using a NMR technique in CD_3OD containing a trace of pyridine-d_5 revealed that there was an equilibration to give about equal amounts of the two diastereoisomers after 15 hr. We could therefore postulate that this equilibration occurred via a form which we would write as the imine-thiocarboxylate intermediate **15**. The intermediacy of **16** could be ruled out, because no deuterium exchange at the 7 position was observed.

Contrary to the instability against bases, **12** was found to be fairly stable under acidic conditions, and owing to this favorable property, we were able to remove the benzyl protective group by using $AlCl_3$ according to the method of Shionogi group.[11] The free acid **2** ($R^1 = CH_2OC_6H_5$) so obtained was similarly unstable under basic conditions and proved to be short alive even in a neutral buffer (pH 7) (half-life time, < 10 min).

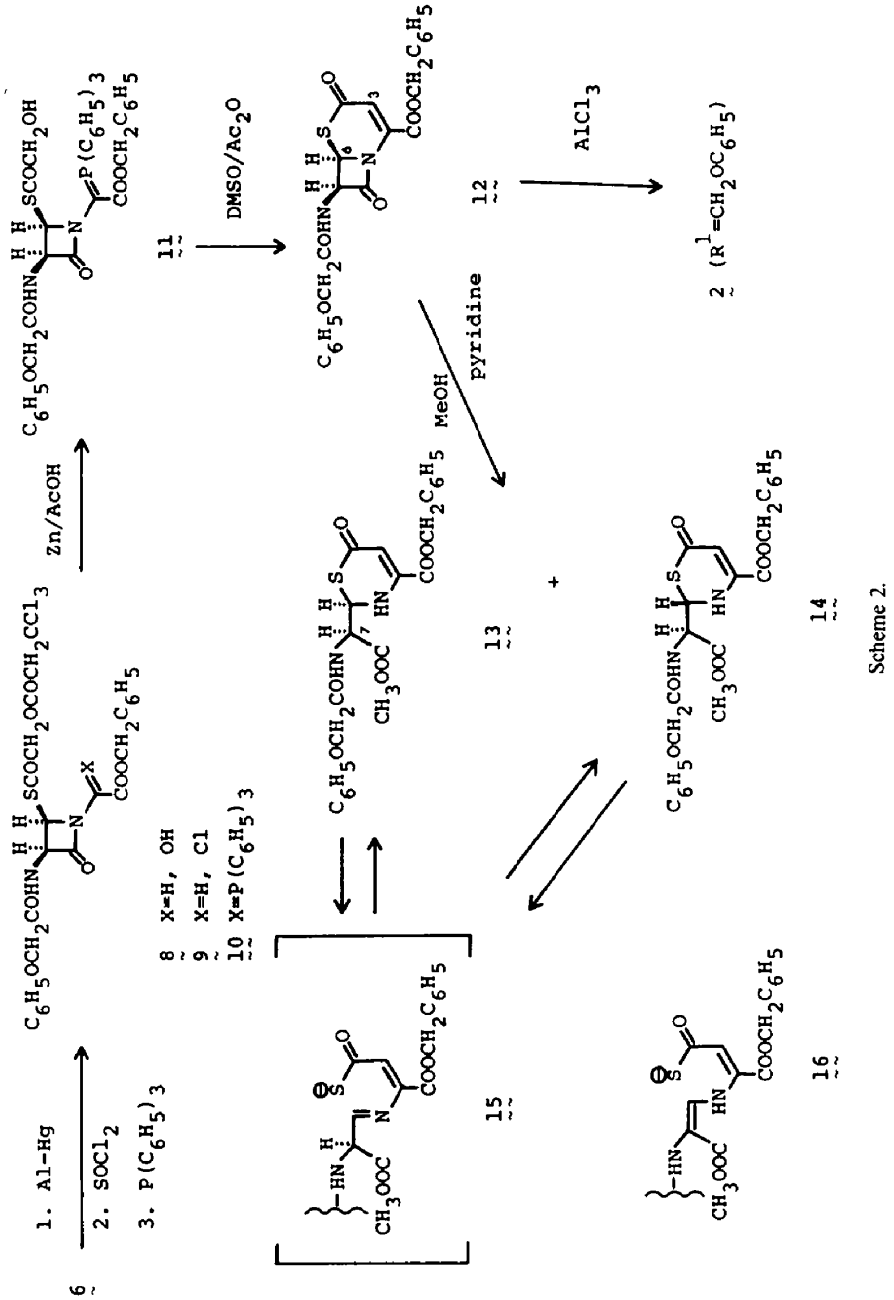
Antibacterial activity of **2** ($R^1 = CH_2OC_6H_5$) was found to be not significant under the test conditions (pH 6.8 ~ 7.0). This was probably due to the instability of the 2-oxocephem nucleus itself as described above. We are now seeking more stable members of this class of compounds.

EXPERIMENTAL

M.ps were determined on a Thomas–Hoover capillary m.p. apparatus and were uncorrected. IR spectra were taken on a Hitachi 260-10 spectrophotometer. ^1H NMR spectra were recorded at 60 MHz on a JNM-PMX 60 NMR spectrometer and at 100 MHz on a JNM-MH 100 NMR spectrometer. UV spectra were recorded on a Hitachi EPS-3T spectrophotometer. Mass spectra (MS) were measured with a Hitachi RMU-6M mass spectrometer.

Benzyl (2R)-2-[(3R, 4R)-3-*phenoxyacetamido*-4-*trichloroethoxycarbonyloxyacetylthio*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-3-*enoate* (**4**).

A suspension of **3**[6] (4.40 g) in CH_2Cl_2 (22 ml) was cooled to −15 and trichloroethoxycarbonyloxyacetyl chloride[7] (4.02 g) was added. The mixture was stirred and a soln of


1. Al-Hg
2. SOCl2
3. P(C6H5)3
Zn/AcOH
DMSO/Ac2O
MeOH
pyridine
AlCl3
8 X=H, OH
9 X=H, Cl
10 X=P(C6H5)3
11
12
13
14
15
16

Scheme 2.

pyridine (1.03 g) in CH_2Cl_2 (5 ml) was added dropwise. After stirring for 15 min, the mixture was poured into a mixture of AcOEt (100 ml) and 2% HClaq (30 ml). The organic layer was separated and washed successively with H_2O, 5% $NaHCO_3$aq and brine. Drying over $MgSO_4$, followed by evaporation, gave 7.00 g of **4** as an oil: IR (CH_2Cl_2) 1760, 1720, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (s, 3 H), 4.55 (s, 2 H), 4.67 (s, 2 H), 4.75 (s, 2 H), 4.8 ~ 5.2 (m, 3 H), 5.47 (dd, J = 5, 8 Hz, 1 H), 6.10 (d, J = 5 Hz, 1 H), 6.8 ~ 7.5 (m, 11 H).

Benzyl 2-[(3R, 4R)-3-*phenoxyacetamido*-4-*trichloroethoxycarbonyloxyacetylthio*-2-*oxoazetidin*-1-*yl*]-3-*methylbut*-2-*enoate* (**5**)

A soln of **4** (4.10 g) in benzene (40 ml) was cooled to 10 and Et_3N (0.17 ml) was added. After stirring for 70 min at room temp, the mixture was washed with 5% HCl aq and H_2O, dried over $MgSO_4$ and evaporated to give an oil, which was chromatographed on silica gel (60 g) eluting with benzene–AcOEt to give 1.24 g (30%) of **5** as an oil: IR (CH_2Cl_2) 1770, 1720 (sh), 1700 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.25 (s, 3 H), 4.55 (s, 2 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.21 (s, 2 H), 5.14 (dd, J = 5.8 Hz, 1 H), 6.01 (d, J = 5 Hz, 1 H), 6.8 ~ 7.4 (m, 10 H).

Benzyl 2-[(3R, 4R)-3-*phenoxyacetamido*-4-*trichloroethoxycarbonyloxyacetylthio*-2-*oxoazetidin*-1-*yl*]-*glyoxylate* (**6**)

(*a*) A soln of **5** (1.18 g) in AcOEt (15 ml) was cooled to −78 and O_3 was bubbled until the starting material was disappeared on tlc. The mixture was purged with N_2 and poured into a mixture of $NaHSO_3$ (5 g) and Na_2SO_3 (1.5 g) in H_2O (50 ml). The organic layer was separated, washed with H_2O, dried over $MgSO_4$ and evaporated to give a crystalline solid, which was washed with ether to give 0.99 g (87%) of **6**: mp 108 ~ 110 °; IR (nujol) 1820, 1760, 1730, 1720, 1660 cm^{-1}; NMR ($CDCl_3$) δ 4.56 (s, 2 H), 4.74 (s, 4 H), 5.33 (s, 2 H), 5.50 (dd, J = 6, 8.5 Hz, 1 H), 6.05 (d, J = 6 Hz, 1 H), 6.8 ~ 7.4 (m, 10 H). (Found: C, 46.09; H, 3.16; N, 4.35; S, 5.27; Cl, 16.46. Calc. for $C_{25}H_{21}N_2O_{10}SCl_3$: C, 46.35; H, 3.27; N, 4.32; S, 4.95; Cl, 16.42%).

(*b*) A soln of **7** (2.44 g) in AcOEt (50 ml) was treated with O_3 in the same manner as described above to give 1.40 g of **6** (60% from **4** via **7**).

Benzyl 2-[(3R, 4R)-3-*phenoxyacetamido*-4-*trichloroethoxycarbonyloxyacetylthio*-2-*oxoazetidin*-1-*yl*]-3-*hydroxybut*-2-*enoate* (**7**)

A soln of **4** (2.60 g) in AcOEt (50 ml) was ozonided in a similar way to that described for preparation of **6**, giving 2.62 g of **7** as an oil: IR (CH_2Cl_2) 1775, 1700, 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.24 (s, 3 H), 4.56 (s, 2 H), 4.77 (s, 2 H), 4.80 (s, 2 H), 5.25 (s, 2 H), 5.21 (dd, J = 5, 9 Hz, 1 H), 6.00 (d, J = 5 Hz, 1 H), 6.8 ~ 7.5 (m, ~11 H).

Benzyl 2-[(3R, 4R)-3-*phenoxyacetamido*-4-*trichloroethoxycarbonyloxyacetylthio*-2-*oxoazetidin*-1-*yl*]-2-*triphenylphosphoranylideneacetate* (**10**)

To a suspension of Al-Hg, prepared from 2 g of Al powder by treating with 0.5% $HgCl_2$aq, in THF (25 ml) was added **6** (1.99 g) and the mixture was cooled to 5 °. To this mixture, AcOH (2 ml) and H_2O (2 ml) was added, and the resulting mixture was stirred for 70 min at the same temp. After filtration of the mixture by the aid of Celite, the filtrate was concentrated and diluted with AcOEt. Washing with dil $NaHCO_3$aq and brine, followed by drying over $MgSO_4$ and evaporation, gave 1.88 g of **8** as a foam: IR (CH_2Cl_2) 3480, 3380, 1780, 1740 (sh), 1690 cm^{-1}.

A mixture of **8** (1.88 g) and 2,6-lutidine (0.52 g) in CH_2Cl_2 (25 ml) was cooled to −40 ° and stirred. To this mixture was added dropwise a soln of $SOCl_2$ (0.57 g) in CH_2Cl_2 (2 ml) and the mixture was stirred for 30 min, during which time the temp was gradually raised to −5 °. The mixture was washed with brine, dried over $MgSO_4$ and filtered.

To the filtrate was added triphenylphosphine (1.57 g) and the mixture was heated to reflux for 5.5 hr. After cooling, the mixture was washed with dil $NaCHO_3$aq and brine, dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (30 g) eluting with benzene–AcOEt to give 1.11 g (43%) of **10** as an oil: IR (CH_2Cl_2) 1760, 1690, 1615 cm^{-1}.

Benzyl 2-[(3R, 4R)-3-*phenoxyacetamido*-4-*hydroxyacetylthio*-2-*oxoazetidin*-1-*yl*]-2-*triphenylphosphoranylideneacetate* (**11**)

To a soln of **10** (1.25 g) in CH_2Cl_2 (15 ml) AcOH (0.7 ml) and Zn dust (1.0 g) was added under ice-bath cooling, and the mixture was stirred for 1 hr at room temp. The mixture was diluted with AcOEt (50 ml) and filtered through a pad of Celite. The filtrate was washed with sat $NaHCO_3$aq and brine, dried over $MgSO_4$ and evaporated to give a crude oil, which was chromatographed on silica gel (10 g) eluting with benzene–AcOEt to give 0.56 g of **11** as an oil. On standing this oil was crystallized. Washing with benzene gave an analytically pure sample: m.p. 128 ~ 132 °; IR (nujol) 3300, 3060 ~ 3180, 1770, 1680, 1600 cm^{-1}. (Found: C, 67.16; H, 4.96; N, 3.66. Calc. for $C_{40}H_{35}N_2O_7PS$: C, 66.84; H, 4.91; N, 3.90%).

Benzyl 7-*phenoxyacetamido*-2-*oxoceph*-3-*em*-4-*carboxylate* (**12**)

To a soln of **11** (oil, 2.04 g) in DMSO (8 ml) was added Ac_2O (8 ml) and the mixture was stirred for 5 hr at room temp. After evaporating the excess Ac_2O *in vacuo*, the residue was poured into a mixture of AcOEt and H_2O. The organic layer was separated and washed with dil $NaHCO_3$aq and brine. Drying over $MgSO_4$ and evaporation gave an oil which was chromatographed on silica gel (24 g) eluting with benzene–AcOEt to give 0.81 g of **12** (65% from **10**) as a crystalline solid: m.p. 130–133 ° (dec); IR (CH_2Cl_2) 3390, 1805, 1735, 1700, 1655 cm^{-1}; NMR (DMSO-d_6) δ 4.63 (s, 2 H), 5.36 (s, 2 H), 5.86 (dd, J = 5, 8 Hz, 1 H), 6.05 (d, J = 5 Hz, 1 H), 6.33 (s, 1 H), 6.9 ~ 7.5 (m, 10 H), 9.36 (d, J = 8 Hz, 1 H); UV λ_{max} (dioxane) 314 nm (ε, 6000), 277 (4200), 270 (4000). (Found: C, 60.53; H, 4.12; N, 6.29; S, 7.08. Calc. for $C_{22}H_{18}N_2O_6S$: C, 60.26; H, 4.13; N, 6.39; S, 7.31%).

Base treatment of **12**

To a stirred soln of **12** (100 mg) in MeOH (20 ml) was added a 1 ml portion of a soln of pyridine (1 drop) in MeOH (5 ml). The starting material gradually disappeared on tlc and a new spot appeared [tlc: silica gel GF_{254} (type 60), Merk, developing with CH_2Cl_2–AcOEt (9:1)]. With continued stirring a second new spot appeared. After disappearance of the starting material (2.5 hr), the solvent was evaporated and the residue was diluted with AcOEt and washed with H_2O. Drying over $MgSO_4$ and evaporation left an oil, which was chromatographed on silica gel (5 g) eluting with CH_2Cl_2 to give 50 mg of **13** (oil) corresponding to the initially formed spot on tlc and 10 mg of **14** (oil) corresponding to the second spot: **13**, $[\alpha]_D$-45 ° (c 0.2, $CHCl_3$); IR (CH_2Cl_2) 1740 (sh), 1735, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.70 (s, 3 H), 4.47 (s, 2 H), 5.04 ~ 5.34 (m, 4 H), 5.98 (d, J = 1 Hz, 1 H), 7.4 ~ 8.4 (m, 11 H), 7.54 (d, J = 7 Hz, 1 H); MS m/e 470 (M^+). **14**, $[\alpha]_D$ + 257 ° (c 0.5, $CHCl_3$); IR (CH_2Cl_2) 1740 (sh), 1735, 1690, 1640 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 3 H), 4.51 (s, 2 H), 5.24 (dd, J = 4, 7 Hz), 5.56 (t, J = 4 Hz, 1 H), 5.94 (d, J = 1 Hz, 1 H), 6.8 ~ 7.4 (m, 11 H), 7.67 (d, J = 7 Hz, 1 H); MS m/e 470 (M^+).

The NMR spectrum of **13** in CD_3OD containing a trace of pyridine-d_5 showed the signals of the ester Me, phenoxyacetyl methylene and C-3 protons at δ 3.70, 4.25 and 5.86, respectively. After 15 hr, the corresponding protons of **14** appeared at δ 3.66, 4.50 and 5.83, respectively, with approximately equal intensities to those of **13**. The C-3 protons of both **13** and **14** were observed with considerably reduced intensities as the result of a deuterium exchange, while the C-6 and C-7 protons of both compounds, which overlapped at δ 5.33 as an AB quartet (J = 7 Hz), retained the original intensities.

7-Phenoxyacetamido-2-oxoceph-3-em-4-carboxylic acid (**2**, $R^1=CH_2OC_6H_5$)

To a soln of **12** (370 mg) in CH_2Cl_2 (15 ml), anisole (1.37 ml) and a soln of $AlCl_3$ (560 mg) in $MeNO_2$ (5 ml) was added under ice-bath cooling, and the mixture was stirred for 30 min at room temp. The mixture was poured into dil HClaq and the organic layer was separated. Washing with brine, followed by drying over $MgSO_4$ and evaporation gave an oil, which was pulverized with isopropyl ether to give 235 mg of **2** ($R^1=CH_2OC_6H_5$) as a solid: mp 158–160°C (dec); IR (nujol) 1810, 1790, 1725, 1650 cm^{-1}; NMR (DMSO-d_6) δ 4.62 (s, 2H), 5.82 (dd, J = 5, 8 Hz, 1H), 6.01 (d, J = 5 Hz, 1H), 6.23 (s, 1H), 6.8 ~ 7.5 (m, 5H), 9.38 (d, J = 8 Hz, 1H). (Found: C, 51.82; H, 3.49; N, 7.76; S, 8.95. Calc. for $C_{15}H_{12}N_2O_6S$: C, 51.72; H, 3.47; N, 8.04; S, 9.20).

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