Nuclear analogs of β-lactam antibiotics. VII. Synthesis of 2-isocephems[1]

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The synthesis of 7-β-phenoxyacetamido-3-methyl-Δ^3-2-isocephem-4-carboxylic acid **14***b* and its corresponding α-sulfoxide **15** and sulfone **17** is described. Treatment of the bismesylates **4***a*, **4***b*, and **10** with hydrogen sulfide triethylamine gave the corresponding 7-β-amino-Δ^3-2-isocephems **12***a–c* which were coupled with phenoxyacetic acid to yield the amides **13***a–c*. Hydrogenolysis of **13***b* and *c* gave the acids **14***a–b* which were active as antibiotics. Compound **14***b* was oxidized to its sulfoxide **15** with sodium metaperiodate and to its sulfone **17** with *m*-chloroperbenzoic acid. Conversion of **13***c* to its sulfoxide **16***b* followed by halogenation gave the 1α-chloro sulfoxide **18** which was converted to the acid **19**. The stereochemical assignments in the 2-isocephem series are discussed.

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On décrit la synthèse de l'acide phénoxyacétamino-7β méthyl-3 Δ^3 isocéphem-2 carboxylique-4 (**14***b*) et de ses sulfoxyde α (**15**) et sulfone **17** correspondants. La réaction des bismésylates **4***a*, **4***b* et **10** avec le sulfure d'hydrogène dans la triéthylamine conduit aux amino-7β Δ^3 isocéphems-2 (**12***a–c*) correspondants qui peuvent réagir avec l'acide phénoxyacétique pour produire les amides **13***a–c*. L'hydrogénolyse de **13***b* et de **13***c* fournit les acides **14***a–b* qui sont actifs comme antibiotiques. On a oxydé le composé **14***b* en sulfoxyde **15** à l'aide du métapériodate de sodium et en sulfone **17** en faisant appel á l'acide métachloroperbenzoique. La transformation de **13***c* en sulfoxyde correspondant **16***b* suivie par une halogénation donne le chloro-1α sulfoxyde **18** qui peut être transformé en acide **19**. On discute des attributions stéréochimiques dans la série des isocéphems-2.

[Traduit par le journal]

In our earlier communications the synthesis of a number of *O*-2-isocephems and *N*-2-isocephems were described (1, 2). We now wish to describe the synthesis of the 2-isocephem system as well as its sulfoxide and sulfone (Fig. 1, X = S, SO, SO_2, Y = CH_2, R = ϕOCH_2, R_2 = H, R_3 = H, CH_3).[4]

To date there has been only one report of a synthesis of the 2-isocephem system by Brunwin and Lowe (4). They have described the synthesis of the 7-α-methyl-7-β-phenylacetamido-2-isocephem-4-carboxylic acid **1** (R_1 = ϕCH_2, R_2 = CH_3, R_3 = H, Y = CH_2, X = S). This material was reported to be devoid of antibiotic activity, which result was not surprising in view of the fact that substitution of the 6 position in penicillins or the 7 position in cephalosporins by a methyl group results in extensive loss of activity (5). In addition Woodward and co-workers have reported the syntheses of a number of cephalosporins containing disulfide linkages (**1**, X = Y = S) in which biological activity has been retained (6).

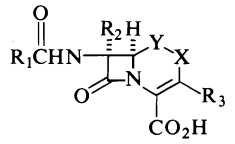

FIGURE 1

Our approach to these compounds is an extension of our synthesis of the *O*-2-isocephem system which we have reported earlier (2*b*). The key intermediates in our synthesis were the bismesylates **4***a*, **4***b*, and **10**. Compounds **4***b* and **10** were prepared in the same manner as **4***a* (1) (Scheme 1). Thus treatment of **2***a* (2*b*) with *p*-nitrobenzyl chloroformate followed by heating

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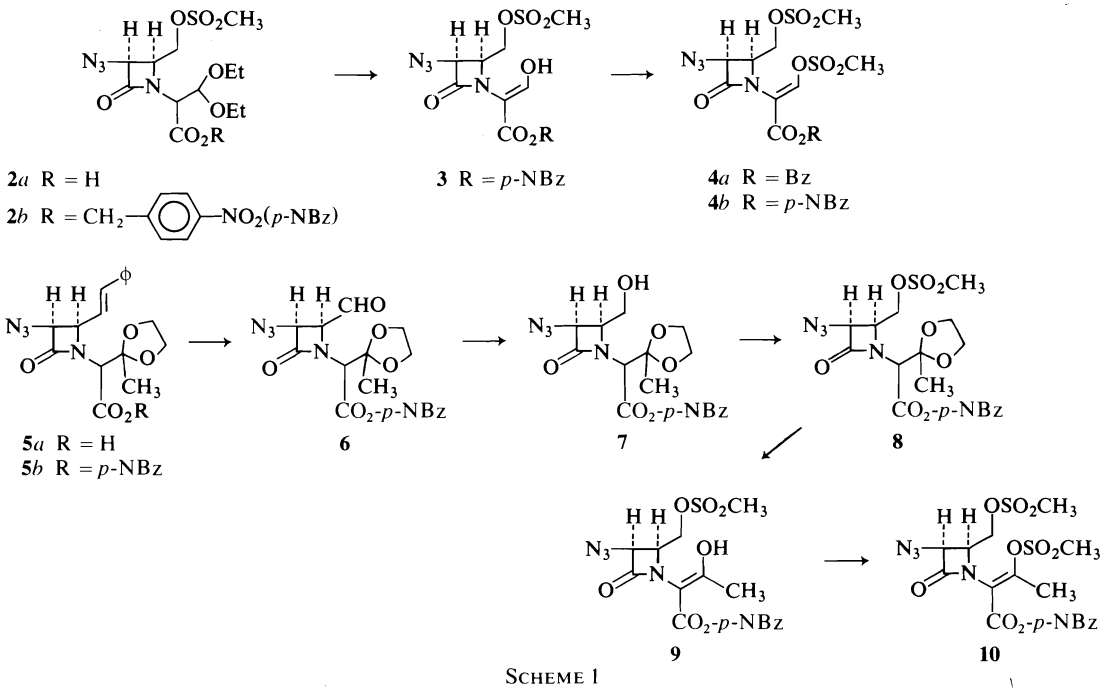
[4]For an explanation of the trivial nomenclature used in this series of papers see ref. 2. Alternatively the nomenclature suggested by Bose might be used. Under such nomenclature the Δ^3-2-isocephem system would be named as a 2-thia-3-octem (3).



SCHEME 1

gave the ester **2***b* in 85% yield. Hydrolysis of the acetal function using 95% trifluoroacetic acid gave the enol **3** in 36% yield. Treatment of the enol **3** with methane sulfonyl chloride and base gave the desired bismesylate **4***b* in 93% yield.

The synthesis of **10** was carried out as follows. Treatment of the acid **5***a* (2*b*) with *p*-nitrobenzyl chloroformate followed by heating as in the preparation of **2***b* gave the ester **5***b* in quantitative yield. Ozonolysis of **5***b* followed by decomposition of the ozonide with dimethyl sulfide gave the aldehyde **6** in 41% yield when isolated. Generally the crude aldehyde was directly reduced with sodium borohydride in tetrahydrofuran at low temperature to give **7**. The crude alcohol was converted to its mesylate **8** which was isolated as a solid in 36% overall yield from **5***a*. Hydrolysis of **8** with trifluoroacetic acid (95%) gave the enol **9** in quantitative yield. Finally treatment of **9** with methane sulfonyl chloride – triethylamine gave the desired bismesylate **10** as an oil (85%).

Our initial experiment on the ring closure of bismesylate to 2-isocephem was carried out on **4***a*. Treatment of **4***a* with potassium acid sulfide in dimethyl sulfoxide gave **11***a* in 44% yield as a crystalline solid. The structure of **11***a* was indicated by its ir, nmr, and uv spectra as well as its correct elemental analysis. The nmr spectrum of **11***a* in $CDCl_3$ was deceptively simple (Table 1) showing a simple doublet of triplets for the C_6 proton and a doublet for the C_1 protons. When the spectrum was recorded in either deuterodimethyl sulfoxide or deuterobenzene the more complex ABX spectrum for these three protons was observed. An analysis of the coupling constants for the C_6, C_1, and C_3 protons of **11***a* permits one to assign each proton as well as to determine the conformation of **11***a* in solution. An examination of Dreiding models of the 2-isocephem system showed that **11***a* could exist in either of two possible conformations A or B (Fig. 2). The coupling constants of $H_{1\alpha}$–H_6 and $H_{1\beta}$–H_6 are 3.5 and 9.5 Hz, respectively, in (C_6D_6). Conformer A is the only conformer consistent with this observation. In addition the 1 Hz long range coupling constant between H_3 and $H_{1\alpha}$ confirms this assignment, these protons being properly aligned in the W configuration in this particular conformation (7). This assignment is in accord with that reached in the *O*-2-isocephem and *N*-2-isocephem systems (1, 2*b*). The uv spectrum of **11***a* showed a band at 303 nm with an extinction coefficient of 13 400. This is in contrast to the value of 296 nm with an extinction coefficient of 4300 reported by Lowe (3) for his 2-isocephem **1** (Fig. 1, X = S, Y = CH_2, R_1 = ϕCH_2, R_2 = Me, R_3 = H). It is apparent

TABLE 1. Nuclear magnetic resonance spectra[a]

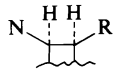
Compd.	Aromatic and vinyl protons		$ArCH_2^-$	CH_3	Other
2*b*[b]	8.14(d, 2H) 7.51(d, 2H) J = 7.5	4.92, 4.97 (d) J = 5.0	5.03(s)	3.04(s) 3.08(s) 1.14(t, J = 7.0) 1.20(t, J = 7.0)	3.60(m, 5H, C*H*CO_2R and CH_2Me) 4.5(m, 4H, C*H*CH_2Mes C*H*$(OEt)_2$)
3	8.10(d, 2H) J = 9.0 7.42(d, 2H) J = 9.0 7.53(s)	4.98(d) J = 5.0	5.23(m)	3.0(s)	4.40(m, C*H*—CH_2OMes, 3H)
4*b*	7.70(s, 1H) 8.10(d, 2H) 7.42(d, 2H) J = 9.0	4.98(d) J = 5.0	5.28(s)	2.97(s) 3.26(s)	4.40(m, 3H)
5*b*[b]	7.58(d) 8.22(d) J = 9 7.38(s, 5H) 6.76, 6.84(d) J = 16.0 6.20(m, 1H)	4.82(m, 2H)	5.20(s) 5.35(s)	1.52(s)	4.34, 4.66(s, C*H*CO_2R) 3.96, 3.98(s, 4H, ketal)
6	8.20(d) 7.54(d) J = 8.5	5.08(d) 4.65(m) J = 5.0	5.30(s)	1.47(s)	4.75(s, C*H*CO_2R) 3.88(m, 4H, ketal) 9.66(d, 1H, C*H*O) J = 4
7[b]	8.24(d) 7.67(d, $J \simeq$ 8)		5.32(s)	1.48	3.90(m, 4H, ketal) 4.4–5.0(m, 6H, CH_2*O*H, C*H*CO_2R, azetidinone protons)
8	8.16(d) 7.54(d) J = 8.5	5.07(d) 4.33(m) $J \simeq$ 5	5.28(s)	1.42(s) 3.0(s)	3.90(4H, m, ketal) 4.65(s, 1H, C*H*—CO_2R) 4.50(m, 3H, C*H*CH_2—OMes)
9	8.16(d) 7.50(d) J = 8.5	5.0(d) 3.88(dd) J = 4.5 J_1 = 4.5 J_2 = 9	5.33(s)	3.03(s) 2.12(s)	4.40(m, 2H, CH_2—OMes)
10	8.10(d) 7.47(d) J = 8.5	4.94(d) J = 4.7	5.28(s)	3.25(s) 2.98(s) 2.53(s)	4.42(m, 3H, C*H*—CH_2—OMes)

TABLE 1 (*Continued*)

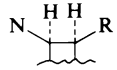
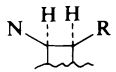
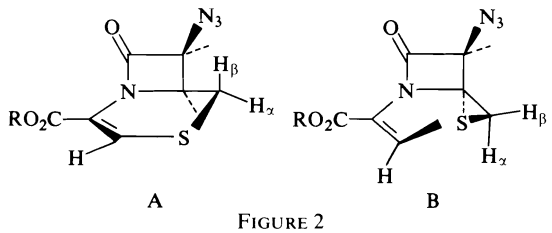
Compd.	Aromatic and vinyl protons			$ArCH_2^-$	CH_3	Other
11*a*	7.41(s, 5H) 7.07(s, 1H)	5.18(d) $J = 5.0$	3.87(dt) $J_1 = 5.0$ $J_2 = 7.0$	5.28(s)		3.04(d, 2H, $J = 7.0$, —CH_2S)
11*a*[c]	7.63(s, 5H) 7.58(bs, 1H)	5.83(d) $J = 5.5$	4.12(ddd) $J_1 = 10.5$ $J_2 = 5.5$ $J_3 = 3.5$	5.39(s)		3.02(dd, 1H, $J_1 = 10.5$ $J_2 = 12.5$) 3.45(dd, 1H, $J_1 = 3.5$, $J_2 = 12.5$)
11*a*[d]	6.15(d, $J_1 = 1$)	3.61(d) $J = 5.0$	2.33(ddd) $J_1 = 9.5$ $J_2 = 5$ $J_3 = 3.5$	4.56(s)		1.79(dd, 1H, $J_1 = 12$, $J_2 = 9.5$ 1.37(ddd, 1H, $J_1 = 12$, $J_2 = 3.5$, $J_3 = 1$
11*b*[c]	8.10(d) 7.58(d) $J = 8.5$ 7.30(s, 1H)	5.59(d) $J = 5.0$	3.95(ddd) $J_1 = 10$ $J_2 = 5.0$ $J_3 = 3.5$	5.30(s)		2.88(dd, 1H, $J_1 = 10$, $J_2 = 13$) 3.34(dd, 1H, $J = 3.5$ $J_2 = 13$)
12*a*	7.32(s, 5H) 6.97(s, 1H)	4.68(d) $J = 5.0$	3.78(dt) $J_1 = 5.0$ $J_2 = 7.0$	5.24(s)		3.00(d, $J = 7.0$, 2H) 1.68(bs, 2H, NH_2)
12*c*	8.12(d) 7.55(d) $J = 8.5$	4.63(d) $J = 5.0$		5.13(d)[e] 5.38(d)[e] $J = 14.0$	2.25(s)	1.67(bs, 2H, NH_2) 3.17(dd, 1H, $J_1 = 9.0$, $J_2 = 12.0$) 2.90(dd, 1H, $J_1 = 4.5$, $J_2 = 12.0$)
13*a*[c]	7.32(s, 5H) 6.7–7.5(m, 5H) 7.0(s, 1H)	5.62(dd) $J_1 = 5.0$ $J_2 = 9.0$	3.87(m)	5.20(s)		4.55(s, 2H, ϕOCH_2—) 3.15(m, 2H) 8.77(d, 1H, NH, $J = 9.0$)
13*b*	8.10(d, 2H) $J = 8.5$ 6.7–7.7(m, 9H)	5.54(dd) $J_1 = 5.0$ $J_2 = 7.0$	3.95(m)	5.13(d)[e] 5.42(d)[e] $J = 13.5$		2.90(m, 2H, CH_2—S) 4.47(s, 2H, ϕOCH_2)
13*c*	8.0(d, 2H) 7.42(d, 2H) $J = 8.5$ 7.57(d, 1H, $J = 7.0$) 6.6–7.3(m, 5H)	5.43(dd) $J_1 = 5.0$ $J_2 = 7.0$	3.90(dt) $J_1 = 5.0$ $J_2 = 9.5$	5.14(bs)	2.23(s)	4.42(s, 2H, ϕOCH_2) 3.06(dd, 1H, $J_1 = 8.5$, $J_2 = 12$) 2.70(dd, 1H, $J_1 = 4.5$, $J_2 = 12$
14*a*[c]	6.7–7.5(6H, m)	5.56(dd) $J_1 = 5$ $J_2 = 9$	3.84(dt) $J_1 = 10$ $J_2 \simeq 5$			4.53(s, 2H, ϕOCH_2) 3.18(dd, $J_1 = 12$, $J_2 = 10$) 2.90(dd, $J_1 = 12$, $J_2 = 5$)

TABLE 1 (*Concluded*)

Compd.	Aromatic and vinyl protons			$ArCH_2^-$	CH_3	Other
14*b*[c]	8.66(d, J = 8, 1H, NH) 6.6–7.5(m, 5H)	5.45(dd) J = 5.0 J = 8.0	3.67(m)		2.12(s)	4.50(s, 2H, ϕOCH_2) 3.25(dd, 1H, J_1 = 9.5, J_2 = 12) 2.75(dd, 1H, J_1 = 4, J_2 = 12)
15[c]	8.80(d, NH, J = 9.0) 6.7–7.4(m, 5H)	5.70(dd) J = 5.0 J = 9.0	4.20(m)		2.18(s)	4.55(s, 2H, ϕOCH_2) 3.15(m, 2H, CH_2—SO)
16*a*[c]	7.38(m, 5H) 6.7–7.5(m, 5H) 7.05(s, 1H)	5.87(dd) J_1 = 5.5 J_2 = 9.0	4.30(m)	5.31(s)		4.58(s, 2H, ϕOCH_2) 3.06(m, 2H, CH_2—SO) 8.78(d, 1H, N*H*, J = 9.0)
16*b*[c]	8.13(d, 2H) 7.61(d, 2H) J = 8.5 6.7–7.4(m, 5H)	5.75(dd) J = 5.0 J = 8.0	4.22(m)	5.42(s)	2.22(s)	4.55(s, 2H, ϕOCH_2) 3.22(m, 2H, CH_2SO—) 8.70(d, 1H, N*H*, J = 8.0)
17[c]	8.70(d, NH, J = 9.5) 6.7–7.4(m, 5H)	5.67(dd) J = 5.0 J = 9.5	4.56(dt) J_1 = 5.0 J_2 = 11 Hz		2.0(s)	4.53(s, 2H, ϕOCH_2) 3.84(dd, 1H, J_1 = 13, J_2 = 11) 3.53(dd, 1H, J_1 = 13, J_2 = 5)
18[c]	8.20(d) 7.65(d) J = 8.5 6.7–7.4(m, 5H)	5.76(dd) J_1 = 6 J_2 = 9	4.85(dd) J = 6 J_2 = 1.5	5.44(s)	2.10(s)	4.68(s, 2H, ϕOCH_2) 6.0(d, 1H, J = 1.5, C*H*Cl) 8.67(d, 1H, N*H*, J = 9)
19[c,f]	6.8–7.5(m, 5H)	5.76(d) J = 6.0	4.86(dd) J_1 = 6.0 J_2 = 1.5		2.05(s)	5.95(d, 1H, J = 1.5, C*H*Cl) 4.75(s, 2H, ϕOCH_2)
20[c]	7.67(s, 5H) 7.50(d, 1H) J = 1.0	6.05(d) J = 5.5	4.47(ddd) J_1 = 3.5 J_2 = 5.5 J_3 = 13	5.50(s)		2.94(dd, 1H, J_1 = 14.5, J_2 = 13) 3.58(ddd, 1H, J_1 = 14.5, J_2 = 3.5, J_3 = 1)
21[c]	7.67(s, 5H) 7.28(d, 1H) J = 1.0	5.88(d) J = 5	4.47(dt) J_1 = 5 J_2 = 12	5.50(s)		3.84(2H, d, J = 12, CH_2—SO_2)

[a]Spectra were recorded at 60 MHz in $CDCl_3$ unless otherwise noted. Coupling constants are in Hz. [b]Mixture of diastereoisomers. [c]DMSO-d_6. [d]Recorded in C_6D_6. TMS external reference in $CDCl_3$. [e]Arms of AB quartet. [f]D_2O exchanged.



A B

FIGURE 2

that the material obtained by these workers cannot have been of much greater than 33% purity inasmuch as it is highly unlikely that substitution of the 7α-proton by methyl would produce such a difference in the extinction coefficient for the two compounds. The values for the extinction coefficients for all 2-isocephems prepared in this work ranged from 11 400 to 15 000.

Reduction of the azido function **11***a* was accomplished using hydrogen sulfide – triethylamine to give **12***a* in 77% yield. The amine was coupled to phenoxyacetic acid using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline(EEDQ) (8) to give **13***a* (78%). Attempted conversion of the ester to the desired acid **14***a* by hydrogenolysis failed due to poisoning of the catalyst. Accordingly it was decided to prepare **14***a* via the *p*-nitrobenzyl ester.

Treatment of **4***b* with hydrogen sulfide and 2.2 equiv. of triethylamine followed by immediate work-up gave the desired 2-isocephem **11***b* in 55.5% yield. Reduction of **11***b* with triethylamine – hydrogen sulfide gave the amine **12***b* in quantitative yield. Coupling of **12***b* and phenoxyacetic acid with EEDQ proceeded in 64% yield to give **13***b*. The preparation of the 3-methyl substituted 2-isocephem was carried out similarly. Thus treatment of the bismesylate **10** with hydrogen sulfide – triethylamine for an extended period (45 min vs. 10 min) accomplished both the ring closure and azide reduction in one step giving the amine **12***c* in 77% yield from **10**. The conversion of the amine **12***c* to its phenoxyacetamide was carried out in the usual fashion to give **13***c* in 74% yield.

Hydrogenolysis of **13***b* over palladium-on-carbon gave the desired acid **14***a* in 40.5% yield. Similarly hydrogenolysis of **13***c* gave **14***b* in 70% yield. The structures of **14***a* and **14***b* were established by their mode of synthesis, elemental analyses, and spectral properties. Both **14***a* and **14***b* exhibited significant antibiotic activity.

Treatment of **14***b* with 1 equiv. of sodium metaperiodate gave the sulfoxide **15** in 77% yield as a single isomer. Alternatively **15** could be prepared by conversion of **13***c* to its sulfoxide **16***b* using *m*-chloroperbenzoic acid followed by reduction of **16***b* to **15** on 10% palladium-on-carbon. The overall yield of **15** from **13***c* was 84%. The material was identical in all respects with that obtained from **14***b*, thus indicating the stereochemistry of the sulfoxide to be the same in each case. Treatment of **14***b* with an excess of *m*-chloroperbenzoic acid gave the sulfone **17** in 25% yield.

Chlorination of the sulfoxide **16***b* using *tert*-butyl hypochlorite gave the monochloro derivative **18** as a single isomer in 67% yield. Compound **18** was converted to the acid by hydrogenolysis over 10% palladium-on-charcoal. Thus **19** was prepared in 56% yield.

Inasmuch as only a single sulfoxide isomer was produced in the oxidations of **14***b* to **15**, **13***a* to **16***a*, and **13***c* to **16***b* the assignment of configuration to these compounds (**15**, **16***a*, **16***b*) rests upon the assumption that oxidation of the sulfur should occur from the least hindered face of the molecule thus producing the α-sulfoxide in each instance. Unfortunately the nmr spectra of compounds **15**, **16***a*, **16***b* did little to resolve the question of their stereochemistry although the down field shift of the C_6 proton was suggestive of the formation of an α-sulfoxide with the pseudoaxial configuration (Fig. 3).

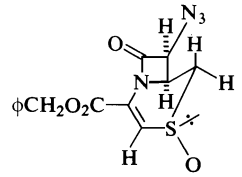
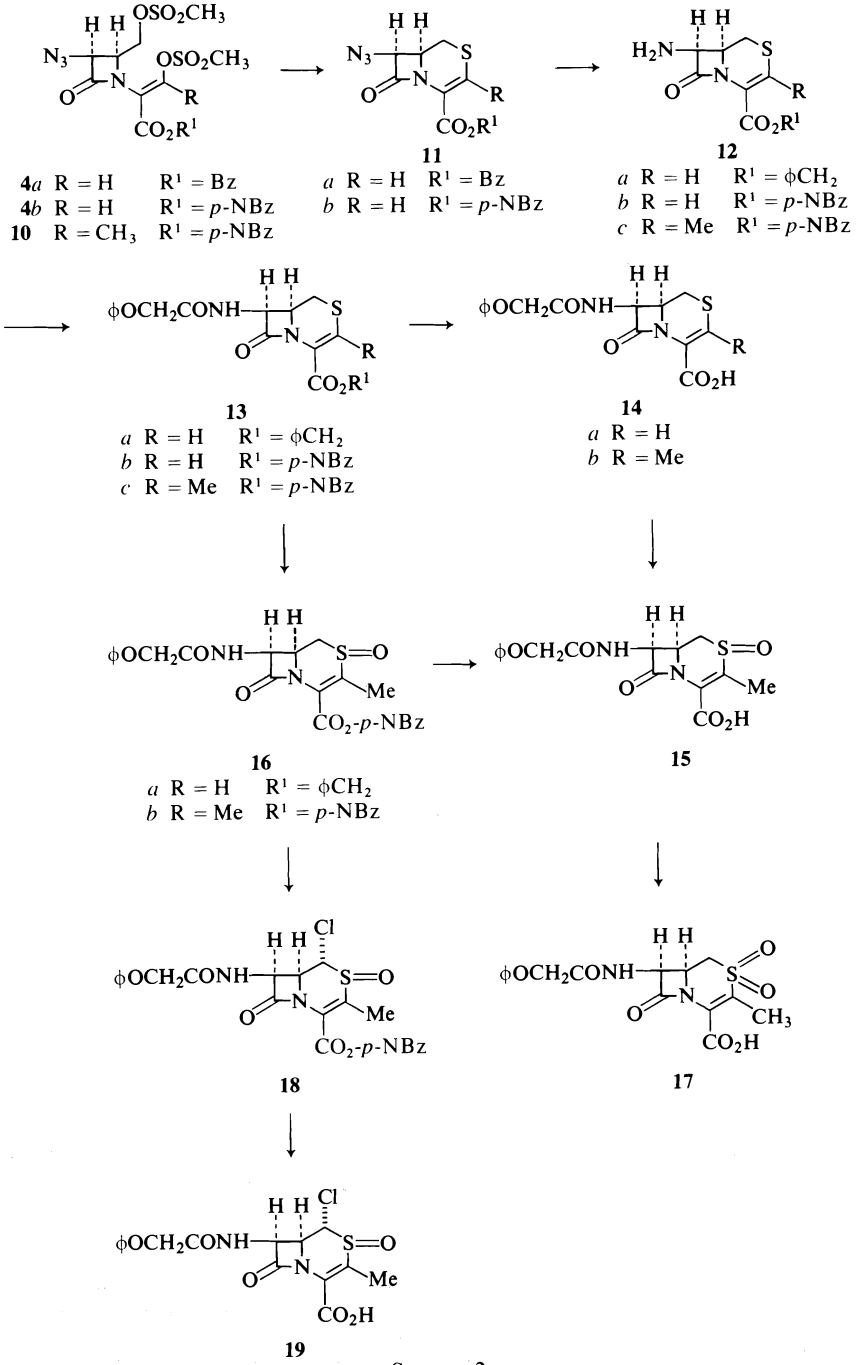


FIGURE 3

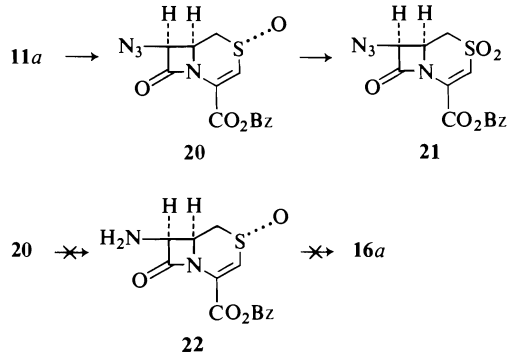
In order to help resolve this question the oxidation of **11***a* to its sulfoxide **20** was carried out. Treatment of **11***a* with 1 equiv. of *m*-chloroperbenzoic acid gave **20** in 74% yield as a single isomer. Prolonged treatment of **11***a* with an excess of *m*-chloroperbenzoic acid gave the sulfone **21** in 86% yield. Several attempts to convert **20** to **16***a* via the amine **22** failed.

A comparison of the nmr spectra of compounds **11***a*, **20**, and **21** permits the configurational assignment to **20** to be made and by inference to **15**, **16***a* and **16***b*. In the nmr spectrum of **20** a down field shift of 0.35 ppm for the C_6 proton was observed typical of the shift usually observed for a proton *syn*-axial to an axial sulfoxide group (9). Conversion of **20** to **21** results



SCHEME 2

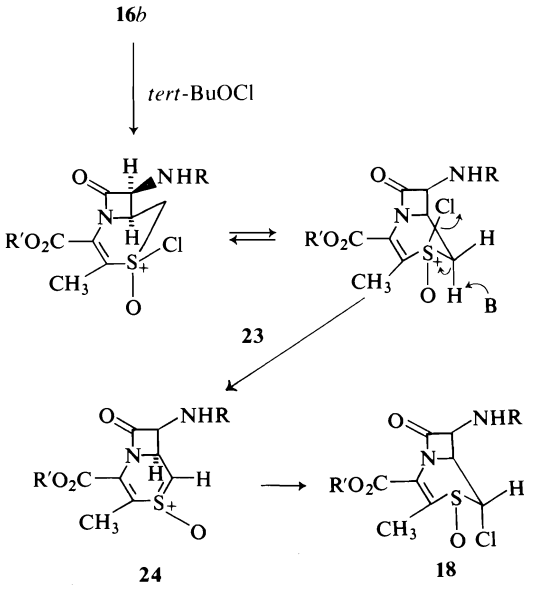
in no shift of the C_6 proton. From the coupling constants for the $C_{1\alpha}$ and $C_{1\beta}$ protons to the C_6 proton both **11***a* and **20** are in the same conformation as shown for **20** in Fig. 3. Thus based on the down field shift of the C_6 proton the α-sulfoxide configuration is assigned to **20**. This is also borne out by the size of the geminal coupling constant for $C_{1\alpha}$ and $C_{1\beta}$ protons in **20** vs. **11***a*. In compound **11***a* J_{gem} = 12.5 Hz while in **20** J_{gem} = 14.5 Hz. The increased J_{gem} is diagnostic



SCHEME 3

of an axial sulfoxide (10) although in the absence of the β-isomer this assignment must be viewed cautiously.

The stereochemical assignment to the α-chlorosulfoxide **18** is uncertain. Recent reports on the stereochemistry of α-halogenation of sulfoxides (11) and the mechanism of the reaction suggest that the chlorination of **17** probably proceeds via the intermediates **23** (Scheme 4) and **24**. A priori one would expect attack of the chloride ion on **24** to proceed from the less hindered α face to give the α-chloro sulfoxide. The nmr spectrum of **18** is in accord with this expectation, there being an ~1.5 Hz coupling constant between the proton α to chlorine and the C_6 proton. The only isomer in which such a small coupling is to be expected is the α-chloro isomer in the conformation shown.



SCHEME 4

While the configuration of the α-chloro group may be thus assigned that of the sulfoxide is less certain. α-Halogenation has been shown to involve both retention and inversion of configuration at sulfur depending on the nature of the sulfoxide and the halogenating agent (11). Spry has reported that α-chlorination of the β-sulfoxide **25** proceeded with retention of configuration at sulfur although no details of the stereochemical assignment were given (12). Inasmuch as this chlorination of **25** probably proceeds via an intermediate **26** similar to **24**, by

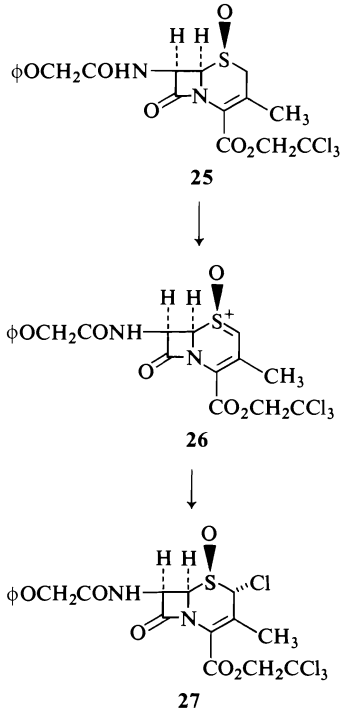


FIGURE 4

analogy the conversion of **16*b*** to **18** may well involve retention at sulfur (Fig. 4).

Experimental

The infrared spectra were recorded on a Unicam SP-200G grating, ir spectrometer. The nmr spectra were determined on a Varian A60-A spectrometer using tetramethylsilane as an internal standard. Melting points are uncorrected and were determined on a Gallenkamp melting point apparatus. The analyses were performed by Micro-Tech Laboratories, Skokie, IL.

*Preparation of **4b***

To a solution of 23.0 g crude acid **2*a*** in 150 ml CH_2Cl_2 at 0–5°C was added 15.4 g *p*-nitrobenzylchloroformate. A solution of 8.5 ml triethylamine in 50 ml CH_2Cl_2 was added dropwise. Vigorous gas evolution and darkening of the solution was observed. The solution was refluxed 15

min and diluted to 300 ml with ether. The solution was washed with 10% HCl (2 × 50 ml), 1% NaOH (1 × 50 ml), and brine (100 ml), dried over Na_2SO_4, and filtered through a pad of activity 3 alumina (~50 g). The filtrate was evaporated to give 26.6 g of crude *p*-nitrobenzyl ester **2***b*.

The crude *p*-nitrobenzyl ester **2***b* was taken up in 100 ml of 95% TFA and evaporated to dryness at 50°C under vacuum (rotary evaporator). This procedure was repeated once and the residual oil taken up in CH_2Cl_2. The solution was washed with brine (3 × 100 ml), dried over Na_2SO_4, filtered, and evaporated. The residual oil was taken up in ether and extracted with 1% NaOH. The aqueous fractions were acidified and extracted into ether – methylene chloride (3 × 100 ml). The extracts were dried over Na_2SO_4, filtered, and evaporated to give 8.0 g of enol **3**; uv (EtOH) λ_{max} 238 (ε 9900).

To a solution of 6.5 g (14.7 mmol) of **3** and 224 ml triethylamine in 75 ml CH_2Cl_2 was added 1.25 ml methanesulfonyl chloride in 10 ml CH_2Cl_2 at 0–5°C. The solution was stirred at 0–5°C for 30 min, washed with 10% HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated to yield 7.08 g (93%) of **4***b*. The nmr and ir spectra of **4***b* were compatible with the assigned structure (as a mixture of geometrical isomers). The oil was used without further purification in the next step.

Preparation of ***10***

A solution of the acid **5***a* (89.5 g, 0.25 mol) and triethylamine (27.8 g, 0.275 mol) in 1.35 ℓ of CH_2Cl_2 was placed in a 2 ℓ flask equipped with magnetic stirrer, a nitrogen inlet, and a dropping funnel. A solution of *p*-nitrobenzylchloroformate (59.3 g, 0.275 mol) in 275 ml of CH_2Cl_2 was added slowly while the reaction mixture was maintained at 0–5°. After completion of the addition, the reaction mixture was maintained at 25°C for 30 min, then heated under reflux until gas evolution ceased (45 min). The resulting solution was washed with brine, 10% HCl (2 × 500 ml), and brine, then dried (Na_2SO_4) and evaporated *in vacuo* (35°C) to give ester **5***b* as an orange oil, 123 g (100%) which was used in subsequent reactions without purification.

A solution of compound **5***b* (123 g, 0.25 mol) in 1.7 ℓ of CH_2Cl_2 was cooled to −78°C and ozone passed through until a blue color persisted (3 h). The excess ozone was flushed out with nitrogen. Dimethyl sulfide (100 ml) was added over 30 min to the solution at −78°C, which was then allowed to come to 25°C over 1 h. The solution was evaporated *in vacuo* and the residue redissolved in 1.7 ℓ of CH_2Cl_2. This solution was washed with brine (2×), dried (Na_2SO_4), filtered through a pad of alumina (500 g, grade III), and evaporated *in vacuo*. The final evaporation was done at 40–45°C and 0.3 Torr for 24 h. The resulting oil, 93.3 g, was shown by nmr to be approximately 35% benzaldehyde and 65% aldehyde **6** (mol%). The oil was triturated with cold ether and the resulting solid was collected by filtration to give 42.5 g of **6** as a white solid, mp 143–146°C; ir (neat) 1785, 1735 cm^{-1}. *Anal.* calcd. for $C_{17}H_{17}N_5O_8$: C 48.69, H 4.09, N 16.70; found: C 48.71, H 4.16, N 16.52.

The crude aldehyde was generally used as such in subsequent reactions.

Sodium borohydride (4.2 g, 0.111 mol) was added in three portions to a stirred solution of crude aldehyde **6** (93.3 g, 0.222 mol) in 775 ml of THF at −5 to −10°C. The reaction was maintained at −5 to −10°C for 2 h, then acidified to p*H* 3 with 10% HCl, saturated with NaCl, and evaporated *in vacuo* (35°C). The resulting residue was mixed with 500 ml of brine and extracted (3 × 400 ml) with CH_2Cl_2. The extracts were dried (Na_2SO_4), filtered through a pad of alumina (500 g, grade III), and evaporated *in vacuo* to give a yellow oil, 80.0 g. The nmr and ir spectra of this oil were consistent with the major portion of the oil being the desired alcohol **7** plus some impurities, including benzyl alcohol.

A solution of 80.0 g (0.19 mol) of alcohol **7** and 30.7 g (0.304 ml) of triethylamine in 825 ml of CH_2Cl_2 was cooled to 0°C and a solution of methane – sulfonyl chloride (32.6 g, 0.285 mol) in 240 ml of CH_2Cl_2 was added over 45 min. The reaction mixture was stirred at 25°C for 5 h, then washed with brine (3 × 500 ml) and 10% HCl (3 × 500 ml). The resulting solution was dried (Na_2SO_4) and evaporated *in vacuo* to a red oil. The oil was crystallized from benzene–ether to give pure mesylate **8** as a colorless solid, 44.5 g, mp 133–136°C. The overall yield from **5***a* to **8** was 36%; ir (Nujol mull) 2110, 1775, 1742 cm^{-1}. *Anal.* calcd. for $C_{18}H_{21}N_5O_{10}S$: C 43.29, H 4.24, N 14.02, S 6.42; found: C 42.85, H 4.38, N 14.24, S 6.35.

A solution of ketal **8** (43.4 g, 87 mmol), trifluoroacetic acid (380 ml), and water (20 ml) was left at 25°C for 2.5 h, then evaporated *in vacuo* at 35°C. The residue was mixed with 400 ml of brine and extracted (3 × 200 ml) with CH_2Cl_2. The organic extract was washed (2 × 100 ml) with brine, dried (Na_2SO_4), and evaporated *in vacuo* to give the enol **9** as a yellow oil, 44.8 g; ir (neat) 2110, 1785, 1755, 1660, 1605 cm^{-1}.

A solution of enol **9** (32.0 g, 74 mmol) and methanesulfonyl chloride (9.32 g, 81.4 mmol) in 950 ml of CH_2Cl_2 was added over 1 h. The reaction mixture was stirred another 1 h at 0°C, then washed with brine (2 × 500 ml), 10% HCl (2 × 500 ml), and brine (500 ml). The solution was dried (Na_2SO_4), filtered through a pad of alumina (200 g, grade III), and evaporated *in vacuo* (35°C) to give the dimesylate **10** as an orange oil, 33.45 g; ir (neat) 2110, 1780, 1735, 1645, 1610 cm^{-1}.

Benzyl 7-β-Azido-Δ³-2-isocephem-4-carboxylate ***11a***

To a solution of 497.5 mg (1.05 mmol) of compound **4***a* in 9 ml dry DMSO at 25°C was added a solution of 160 mg (2.10 mmol) potassium acid sulfide in 5 ml DMSO in a dropwise fashion. As each drop was added a transient green color was observed. After approximately 50% of the KSH solution had been added, the green color faded to yellow (rather than colorless as previously observed). Addition was stopped and the solution was stirred 5 min. The solution was poured into 50 ml of brine to which 10 ml 10% HCl had been added. The solution was extracted with CH_2Cl_2–Et_2O, the extracts washed with water (3 × 50 ml) and brine (1 × 25 ml), dried over Na_2SO_4, filtered, and evaporated to yield 255 mg partially crystalline oil. The oil was passed through 2 g silica gel with CH_2Cl_2 and evaporated. Trituration with ether (5 ml) and filtration gave 145 mg of **11***a*, mp 97°C; ir ($CHCl_3$): 2110, 1782, 1715, 1580 cm^{-1}; uv (EtOH) λ_{max} 303 (ε 13 400). *Anal.* calcd. for $C_{14}H_{12}N_4O_3S$: C 53.15, H 3.82, N 17.71; found: C 53.19, H 3.75, N 17.94.

p-Nitrobenzyl 7-β-Azido-Δ³-2-isocephem-4-carboxylate ***11b***

Into a solution of 2.90 g (5.6 mmol) bismesylate **4***b* in 50 ml CH_2Cl_2 was bubbled H_2S gas for 3 min. To this

was added 1.35 g (13.3 mmol) triethylamine in 10 ml CH_2Cl_2 dropwise over 10 min. The solution was purged with a stream of N_2 and washed with 10% HCl, $NaHCO_3$, and brine. The solution was dried over Na_2SO_4 and concentrated. Trituration of the oil with CH_2Cl_2 induced crystallization. Filtration gave 1.12 g (55.5%) crystalline **11***b*, mp 187.5–188.5°C; uv (EtOH) λ_{max} 303 (ε 14 970); ir ($CHCl_3$): 2110, 1782, 1720, 1608, 1573, 1525 cm^{-1}. *Anal.* calcd. for $C_{14}H_{11}N_5O_5S$: C 46.53, H 3.07, N 19.38, S 8.87; found: C 46.69, H 3.07, N 19.65, S 9.18.

Benzyl 7-β-Amino-Δ³-2-isocephem-4-carboxylate ***12a***

To a solution of 316 mg (1 mmol) of **11***a* in 20 ml methylene chloride was added 101 mg (1 mmol) triethylamine. A stream of hydrogen sulfide was passed through the solution for 3 min and the solution was let stand 1 h at 25°C. The solvent was evaporated at reduced pressure and the residue was partitioned between 10% hydrochloric acid and ether. The aqueous layer was neutralized using sodium bicarbonate and extracted with methylene chloride. The extracts were dried over sodium sulfate and evaporated to yield 223 mg (77%) of **12***a*, mp 119–120°C, recrystallized from benzene; ir ($CHCl_3$): 3400, 1770, 1715, 1577 cm^{-1}; uv (EtOH) λ_{max} 305 (ε 14 060). *Anal.* calcd. for $C_{14}H_{14}N_2O_3S$: C 57.91, H 4.86, N 9.65, S 11.04; found: C 58.32, H 4.81, N 9.70, S 11.17.

p-Nitrobenzyl 7-β-Amino-Δ³-2-isocephem-4-carboxylate ***12b***

Reduction of 525 mg (1.45 mmol) of **11***b* in methylene chloride using triethylamine – hydrogen sulfide as in the above example gave 486 mg (100%) of **12***b*, mp 181.5–183°C recrystallized from acetonitrile–ether; ir ($CHCl_3$): 1775, 1720, 1610, 1580, 1530 cm^{-1}; uv (EtOH) λ_{max} 301 (ε 15 200). *Anal.* calcd. for $C_{14}H_{13}N_3O_5S$: C 50.14, H 3.91, N 12.53, S 9.56; found: C 49.85, H 3.85, N 12.67, S 9.59.

p-Nitrobenzyl 3-Methyl-7-β-amino-Δ³-2-isocephem-4-carboxylate ***12c***

Hydrogen sulfide was passed into a solution of dimesylate **10** (4.4 g, 8.24 mmol) in 90 ml of CH_2Cl_2 at 0–5°C for 15 min. With the temperature maintained at 0–5°C, a solution of triethylamine (2.5 g, 24.7 mmol) in 50 ml of CH_2Cl_2 was added over 10 min. The reaction mixture was stirred at 25°C for 45 min. The resulting solution was washed with brine (2 × 100 ml), dried (Na_2SO_4), treated with charcoal, and evaporated *in vacuo* to give a yellow oil. The oil was dissolved in a minimum volume of CH_2Cl_2 (an insoluble gum was removed by filtration) and saturated with HCl (gas). Ether was added to near opalescence and the solution was cooled to 0°C. The hydrochloride salt of **12***c* was obtained as a pale yellow solid, 2.5 g (77%), mp 194–195°C (dec.). The amine **12***c* was stored as its HCl salt; the free base was prepared as follows. The salt was suspended in water, $NaHCO_3$ added until basic, and the mixture extracted (3×) with CH_2Cl_2. The extracts were dried, treated with charcoal, and evaporated *in vacuo* to give the free base **12***c* as a pale yellow foam; ir (Nujol mull on HCl salt): 1782, 1695, 1610, 1580, 1530 cm^{-1}. *Anal.* calcd. for $C_{15}H_{15}N_3O_5S \cdot HCl$: C 46.70, H 4.18, N 10.89, Cl 9.19, S 8.31; found: C 46.50, H 4.20, N 10.85, Cl 9.08, S 8.18.

Benzyl 7-β-(Phenoxyacetamido)-Δ³-2-isocephem-4-carboxylate ***13a***

To a solution of 223 mg (0.77 mmol) of **12***a* in 25 ml methylene chloride was added 123 mg (0.81 mmol) phenoxyacetic acid followed by 200 mg (0.81 mmol) EEDQ. The solution was let stand 18 h at 25°C and washed with 10% hydrochloric acid, 5% sodium bicarbonate, water, and brine. After drying over sodium sulfate, the extracts were evaporated and the residual oil triturated with ether–chloroform. There was obtained 254.5 mg (78%) of **13***a*, mp 184–185°C with decomposition; ir ($CHCl_3$): 3430, 3350, 1770, 1712, 1690, 1601, 1590, 1575, 1530, 1500 cm^{-1}; uv (EtOH) λ_{max} 303 (ε 12 850). *Anal.* calcd. for $C_{22}H_{20}N_2O_5S$: C 62.26, H 4.75, N 6.60, S 7.55; found: C 62.32, H 4.98, N 6.63, S 7.50.

p-Nitrobenzyl 7-β-(Phenoxyacetamido)-Δ³-2-isocephem-4-carboxylate ***13b***

The coupling of 335 mg (1 mmol) of **12***b* with phenoxyacetic acid using EEDQ as in the above example gave 295.7 mg (64%) of **13***b*, mp 180°C after recrystallization from benzene; ir ($CHCl_3$): 3420, 1778, 1720, 1692, 1598, 1573, 1523, 1492 cm^{-1}; uv (EtOH) λ_{max} 302.5 (ε 15 060). *Anal.* calcd. for $C_{22}H_{19}N_3O_7S$: C 56.28, H 4.07, N 8.95, S 6.83; found: C 55.93, H 4.06, N 9.05, S 6.62.

p-Nitrobenzyl 3-Methyl-7-β-(phenoxyacetamido)-Δ³-2-isocephem-4-carboxylate ***13c***

Treatment of 4.0 g (11.4 mmol) of **12***c* with phenoxyacetic acid and EEDQ as in the above example gave after work-up **13***c* as a foam. The foam was recrystallized from benzene to yield 4.75 g (74%) of **13***c* as a beige solid; ir (Nujol mull): 3340, 3310, 1755, 1715, 1680, 1600, 1590, 1575 cm^{-1}. *Anal.* calcd. for $C_{23}H_{21}N_3O_7S$: C 57.14, H 4.38, N 8.69; found: C 57.46, H 4.44, N 8.20.

7-β-(Phenoxyacetamido)-Δ³-2-isocephem-4-carboxylic Acid ***14a***

Compound **13***b* (469 mg, 0.001 mol) in 2 ml DMF and 20 ml methanol (to which 5 drops 10% HCl had been added) were stirred with 700 mg of 10% Pd/C at atmospheric pressure and ambient temperature (20°C) under hydrogen. Rapid uptake of 3 equiv. of hydrogen was observed (35 min). The uptake of the fourth equivalent of hydrogen required an additional 2 h. The suspension was filtered through Celite (filter cake washed with CH_2Cl_2) and the filtrate evaporated. The residue was taken up in 50 ml CH_2Cl_2 and the filtrate evaporated. The solution was dried over Na_2SO_4 and filtered. The filtrate was evaporated to give a yellow solid. Trituration with 5 ml ether and filtration gave 135 mg (40.5%) of **14***a*, mp 209–210°C with decomposition (after recrystallization from acetone–ether); ir (KBr disc): 2400–3600, 3340, 1770, 1750, 1665, 1575 cm^{-1}; uv (EtOH) λ_{max} 298 (ε 12 750). *Anal.* calcd. for $C_{15}H_{14}N_2O_5S$: C 53.87, H 4.22, N 8.37, S 9.59; found: C 53.43, H 4.23, N 8.45, S 9.38.

3-Methyl-7-β-(Phenoxyacetamido)-Δ³-2-isocephem-4-carboxylic Acid ***14b***

A solution of **13***c* (2.0 g, 3.57 mmol) in dioxane (50 ml) and methanol (25 ml) containing 1.0 g of 10% palladium-on-charcoal was hydrogenated on a Parr shaker at 25°C and 50 psi for 3 h. The catalyst was filtered off and the solution evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate (EtOAc) and washed with 10% HCl (3×), then with brine. The aqueous layers were extracted (2×) with EtOAc and each extract washed with brine. The combined organic layers were treated with charcoal and evaporated *in vacuo* to a solid. The solid was dissolved in very dilute $NaHCO_3$ containing slightly more

than 1 equiv. of base. This aqueous solution was washed with EtOAc, acidified to p*H* 2 with 10% HCl, and extracted 2× with EtOAc. The organic solution was dried (Na_2SO_4) and evaporated *in vacuo* to give the acid **14***b* as an off-white solid, 865 mg (70% yield). The product could be recrystallized from EtOAc, mp 219–220°C; ir (Nujol mull): 3340, 1755(s), 1745, 1705, 1660, 1590 cm^{-1}; uv (MeOH) λ_{max} 294 (ε 11 400). *Anal.* calcd. for $C_{16}H_{16}N_2O_5S$: C 55.16, H 4.63, N 8.04, S 9.20; found: C 55.03, H 4.62, N 7.98, S 9.07.

Benzyl 2-Oxido-7-β-(Phenoxyacetamido)-Δ³-2-isocephem-4-carboxylate ***16a***

To a solution of 215 mg (0.51 mmol) of **13***a* in 15 ml of methylene chloride was added 107 mg (~0.51 mmol) of *m*-chloroperbenzoic acid in 5 ml methylene chloride at 0–5°C over 15 min. The solution was stirred 15 min at 25°C and washed with 5% sodium bicarbonate solution. The solution was dried over sodium sulfate and concentrated to yield a semisolid which crystallized on trituration with ether to give 157.0 mg (70%) of **16***a*, mp 203–204°C; ir ($CHCl_3$): 3410, 1795, 1735, 1695, 1609, 1595, 1520, 1495 cm^{-1}. *Anal.* calcd. for $C_{22}H_{20}N_2O_6S$: C 59.98, H 4.58, N 6.36, S 7.27; found: C 59.91, H 4.40, N 6.44, S 7.05.

p-Nitrobenzyl 2-Oxido-3-methyl-7-β-(phenoxyacetamido)-Δ³-2-isocephem-4-carboxylate ***16b***

A solution of *m*-chloroperbenzoic acid (103 mg, containing 0.505 mmol) in 11 ml of CH_2Cl_2 was added over 75 min to a stirred solution of **13***b* (280 mg, 0.50 mmol) in 11 ml of CH_2Cl_2 at 0°C. After a further 15 min at 0°C, the solution was washed (3×) with 10% $NaHCO_3$ containing several drops of Na_2CO_3, dried, and evaporated *in vacuo* to give the sulfoxide **16***b* as a colorless foam, 281 mg.

2-Oxido-3-methyl-7-β-(phenoxyacetamido)-Δ³-2-isocephem-4-carboxylic Acid ***15***

From ***14b***

The isocephem **14***b* (454 mg, 1.30 mmol), 45 ml of water, $NaHCO_3$ (110 mg, 1.31 mmol), and sodium metaperiodate (280 mg, 1.30 mmol) were stirred together at 25°C for 24 h. The resulting solution was saturated with NaCl and 10% HCl added until p*H* 2 reached. This mixture was extracted (3×) with EtOAc containing some MeOH. The combined extracts were washed with brine, dried, and evaporated *in vacuo* to give the sulfoxide **15**, 363 mg (77% yield), as a beige solid. Recrystallization from EtOAc–MeOH gave a colorless solid, mp 229–232°C (dec.); ir (Nujol mull): 3360, 3310, 1775, 1720, 1635, 1600, 1595, 1545, 1495 cm^{-1}; uv (MeOH) λ_{max} 270, 275 (ε 9100). *Anal.* calcd. for $C_{16}H_{16}N_2O_6S$: C 52.75, H 4.43, N 7.69, S 8.80; found: C 52.65, H 4.45, N 7.64, S 8.60.

From ***16b***

A mixture containing the sulfoxide ester **16***b* (280 mg, 0.485 mmol), THF (28 ml), dioxane (14 ml), MeOH (2.8 ml), and 10% palladium-on-charcoal was hydrogenated on a Parr shaker at 25°C and 50 psi for 4 h. The catalyst was filtered off and the solution evaporated *in vacuo*. The residue was mixed with EtOAc and ½ ml of 10% HCl and enough MeOH added to make a nearly homogeneous solution. The filtered solution was extracted (2 × 20 ml) with 1% $NaHCO_3$. The aqueous layer was acidified with 10% HCl, saturated with NaCl, and extracted (2×) with EtOAc/MeOH. The organic layers were washed with brine, dried, and evaporated *in vacuo* to give 149 mg (84%) of **15**, the ir and nmr spectra of which were identical with the sample prepared from **14***b*.

2,2-Dioxo-3-methyl-7-β-(phenoxyacetamido)-Δ³-2-isocephem-4-carboxylic Acid ***17***

A solution of *m*-chloroperbenzoic acid (542 mg, containing 2.66 mmol) in 5 ml of EtOAc was added to a slurry of isocephem **14***b* (440 mg, 1.26 mmol) in 44 ml of EtOAc. The mixture was stirred at 25°C for 40 h, then evaporated to dryness under a nitrogen stream. The resulting solid was triturated with small volumes of EtOAc several times, then recrystallized from EtOAc–MeOH (3×) to give the sulfone **17** as a colorless solid, mp 203–204°C (dec.), 118 mg (25% yield); ir (Nujol mull): 3380, 2400–3600, 1795, 1735, 1665, 1620, 1600, 1590, 1520, 1495 cm^{-1}; uv (MeOH) λ_{max} 267 (ε 11 100). *Anal.* calcd. for $C_{16}H_{16}N_2O_7S$: C 50.53, H 4.24, N 7.37, S 8.43; found: C 50.38, H 4.25, N 7.38, S 8.60.

p-Nitrobenzyl 1-α-Chloro-2-oxido-3-methyl-7-β(phenoxyacetamido)-Δ³-2-isocephem-4-carboxylate ***18***

To a slurry of sulfoxide **16***b* (889 mg, 1.78 mmol) and potassium acetate (465 mg, 4.74 mmol) in 70 ml of CH_2Cl_2 at 0°C was added a solution of *tert*-butyl hypochlorite (0.213 ml, 1.92 mmol) in 4 ml of CH_2Cl_2. The mixture was stirred at 0°C for 3.5 h. Water (70 ml) was added and the mixture shaken and separated. The water was extracted with more CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to give a yellow oil. A $CHCl_3$ solution of the oil deposited crystals on standing 24 h. The mother liquors were chromatographed on silica (15% water) with $CHCl_3$, the second fraction giving desired product and the third fraction, starting material. Total yield of chlorosulfoxide **18** was 635 mg (67%). The product could be recrystallized from $CHCl_3$ to give material with mp 182–184°C (dec.); ir (Nujol mull): 3330, 1780, 1733, 1675 cm^{-1}. *Anal.* calcd. for $C_{23}H_{20}ClN_3O_8S$: C 51.74, H 3.78, N 7.87, Cl 6.63, S 6.01; found: C 51.47, H 3.66, N 7.74, Cl 6.48, S 5.85.

1-α-Chloro-2-oxido-3-methyl-7-β-(phenoxyacetamido)-Δ³-2-isocephem-4-carboxylic Acid ***19***

A mixture of **18** (600 mg, 1.125 mmol), 10% palladium-on-charcoal (600 mg), dioxane (30 ml), and methanol (15 ml) was hydrogenated on a Parr shaker at 50 psi and 25°C for 3.5 h. The catalyst was filtered off and the filtrates evaporated *in vacuo*. The resulting oil was dissolved in ethyl acetate and this solution was washed with 10% HCl (2 × 50 ml) and brine (2 × 50 ml) and then extracted with 10% $NaHCO_3$ (3 × 50 ml). The basic extracts were washed with ether (2×), acidified to p*H* 3 with 10% HCl, and extracted with ethyl acetate (3 × 75 ml). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting oil was crystallized from ethyl acetate to give the acid **19**, 250 mg (56%), mp 204–205°C (dec.); ir (Nujol mull): 3400, 3600–2400, 1790, 1778, 1710, 1670, 1660 cm^{-1}; uv (MeOH) λ_{max} 275 (ε 9500) 286 (ε 9400). *Anal.* calcd. for $C_{16}H_{15}ClN_2O_6S$: C 48.19, H 3.79, N 7.02, Cl 8.89, S 8.04; found: C 48.11, H 3.77, N 6.95, Cl 8.77, S 7.94.

Benzyl 2-Oxido-7-β-azido-Δ³-2-isocephem-4-carboxylate ***20***

To a solution of 2.005 g (6.35 mmol) of compound **11***a*

in 45 ml $CHCl_3$ at 0–5°C was added 1.35 g (6.45 mmol) of *m*-chloroperoxybenzoic acid (85%) in 25 ml $CHCl_3$ over 15 min. Thin layer chromatography showed complete reaction after addition was complete. The solution was stirred 15 min, diluted to 400 ml with $CHCl_3$, extracted with Na_2CO_3 (2 × 50 ml of saturated aqueous solution), dried over Na_2SO_4, and concentrated to give compound **20** as a solid. Trituration with 25 ml Et_2O and filtration gave 1.5 g sulfoxide **20** (74%); mp 159–160°C (dec.) recrystallized from $CHCl_3$–Et_2O; ir ($CHCl_3$) 2110, 1800, 1738, 1580 cm^{-1}; uv (EtOH) λ_{max} 279 (ε 12 100). *Anal.* calcd. for $C_{14}H_{12}N_4O_4S$: C 50.59, H 3.64, N 16.86; found: C 50.28, H 3.34, N 16.81.

Benzyl 2,2-Dioxido-7-β-azido-Δ^3-2-isocephem-4-carboxylate ***21***

To a solution of 158 mg (0.5 mmol) of **11***a* in 20 ml methylene chloride was added 220 mg (1.10 mmol) of 85% *m*-chloroperbenzoic acid. The solution was stirred at 25°C for 18 h and then washed with 5% sodium bicarbonate solution. The organic phase was dried over sodium sulfate and evaporated to give an oil which crystallized on trituration with ether. Filtration gave 150 mg (86.5%) of **21**, mp 113.5–114.5°C after recrystallization from chloroform–ether; ir ($CHCl_3$) 2110, 1803, 1740 cm^{-1}; uv (EtOH) λ_{max} 274 (ε 10 100). *Anal.* calcd. for $C_{14}H_{12}N_4O_5S$: C 48.27, H 3.47, N 16.09, S 9.21; found: C 48.38, H 3.31, N 16.08, S 9.42.

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