Structure and Stereochemistry of Isomeric Penam and Cepham Derivatives[1]

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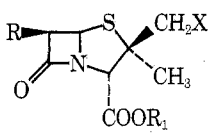
The ^1H and ^{13}C NMR spectra of a number of isomeric penam and cepham derivatives are reported. On the basis of these data assignments of structure and stereochemistry of penams and cephams have been made. In addition an independent study by X-ray diffraction has also confirmed the structure and stereochemistry of the title compounds.

The synthesis and chemical transformations of the title compounds are described in the preceding communication.[2] Working with these isomers, we, as well as others,[3] have encountered difficulties in distinguishing the structures and stereochemistry of isomeric penams and cephams. A more extended study of the nuclear magnetic resonance (NMR) spectra of these compounds has led to the development of additional methods that are useful in making structural and configurational distinctions in these systems.

The major difference between the penams (1 and 2), the cephams (3), and cephems (4) is in the size of the heterocyclic ring attached to the four-membered azetidinone. The β-lactam is easily characterized by the carbonyl stretching frequency between 1778 and 1806 cm^{-1} in the infrared spectrum. The cephem system (4) is also easily recognized through the carbonyl bands of the ir spectrum, as well as through proton chemical shifts and absence of the 4-H singlet in the ^1H NMR spectrum. The ir and ^1H NMR spectra of compound types 1, 2, and 3, however, are very similar. In the ^1H NMR spectra, for example, one observes for all three structural types (1) a methyl singlet; (2) an AB system due to the methylene group; (3) a one-proton singlet of the 3-H or 4-H; and (4) the pattern of resonances characteristic of the two methine proton resonances of the azetidinone ring. Attempts to distinguish between penam and cepham structures by arguments based upon proton chemical shifts and long-range proton–proton coupling are seldom successful. To overcome these difficulties, we have undertaken a study of the ^{13}C NMR spectra of these compounds.



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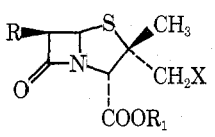

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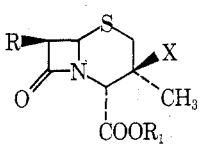

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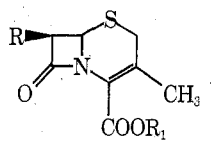

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The ^{13}C NMR spectroscopy has been shown to be useful in the elucidation of the structural problems of a different type of penicillins and cephalosporins.[4,5] The first step in interpreting the ^{13}C NMR spectra of these compounds is to identify those resonances due to the substituents R and R_1. This is generally easily effected through comparisons of these spectra to those of simple model compounds. Of the remaining resonances of the nucleus of the penam or cepham system (cf. Tables III and IV), three can be identified on the basis of their chemical shifts as being due to the carbonyl carbons. These resonances show a surprising degree of variation throughout these series, and at present we have no reliable means of assigning them specifically. Because of the long T_1 values characteristic of carbonyl carbons,[6] these resonances show misleading peak intensities and are occasionally difficult to detect, especially when only limited amounts of material are available. In compounds with structure 4 two resonances in the range typical of olefinic carbons make the recognition of this structural type straightforward.

In the upfield region of compounds of structures 1–3 one observes six carbon resonances. Through the use of off-resonance decoupling[6] one can easily assign these resonances to nonprotonated, methine, methylene, and methyl carbons. The methyl carbon resonances occur in the same range of chemical shifts (20–30 ppm) in structures 1–4, and provide no reliable guide in distinguishing between these structural types. In cepham structures of type 3 the nonprotonated carbon is directly substituted by X. Because of the widely varying α effects[6] of the X substituents, this leads to wider variation in the shifts of the C-3 resonances of 3 than observed for the C-2 resonances of 1 and 2. Despite this fact the chemical shift of the nonprotonated carbons is not a reliable guide in differentiating penam and cepham systems.

In fact, these two structural types are most easily distinguished through the chemical shift of the methylene carbons. In penam systems (1 and 2) the methylene carbon is directly substituted by X and is, therefore, deshielded to a degree which is largely dependent upon the electronegativity of this substituent.[7] In cepham systems, however, the only electronegative substituent on the methylene carbon is sulfur, which is known[7] to have an unusually small α effect. As a result, the methylene resonances of structural type 3 come into resonance in the chemical shift range 35 ± 4 ppm, while those of 1 or 2 are found below 42 ppm.

In the proton NMR spectra of these compounds, it is generally possible to assign the resonances of the methine protons specifically (cf. Tables I and II). Used in conjunction with selective proton decoupling,[6] these assignments can be used to identify specifically the three methine carbon resonances. Tables III and IV show that the carbon substituted by R has a relatively constant shift in all structural types (1–4). The other two methine carbons resonate at lower field in the penams than their analogs in the cephams. This parallels results from carbohydrate chemistry,[8] where a general deshielding of carbons in five-membered furanose systems relative to the six-membered pyranoses has been noted. It would appear, then, that the chemical shifts of the methine carbons of the thiazolidine

Table I
^{1}H NMR Data of Penam Derivatives

Compd No.[a]	R[b]	X	2α-CH_3	2β-CH_3	2α-CH_2X	2β-CH_2X	3-H	5-H	6-H
1a	Ft	Cl		1.93	3.77, 3.91 (11.5)		4.78	5.61 (4.5)	5.70 (4.5)
1b	Ft	Br		1.97	3.7, 3.9 (11.5)		4.8	5.6	5.6
1a	Ft	OAc		1.83	4.15, 4.29 (12)		4.71	5.57 (4.5)	5.64 (4.5)
1a	Ft	NO_3		1.88	4.69		4.79	5.60 (4.5)	5.71 (4.5)
2a	Ft	Cl	1.58			3.59, 4.51 (11.8)	5.14	5.74	5.74
2a	Ft	OAc	1.46			4.30, 4.68 (12)	5.0	5.63	5.63
2a	Ft	NO_3	1.53			4.72, 5.16 (11.5)	4.94	5.77	5.74
2b	Ft	Cl	1.57			3.68, 4.52 (12)	5.14	5.73	5.73
2b	Ft	Br	1.60			3.68, 4.50 (11.5)	5.30	5.80	5.80
2b	V	Cl	1.52			3.50	5.08	5.72	5.72
2c	Ft	Cl	1.51			3.62, 4.43 (12)	5.12	5.70	5.70
2c	Ft	NO_3	1.43			4.69, 5.16 (11.5)	4.95	5.77	5.77

[a] In structure numbers, a represents compounds in which $R_1 = CH_3$, while b and c indicate that R_1 is *p*-nitrobenzyl and *p*-methoxybenzyl, respectively. [b] Abbreviations used are Ft = phthalimido and V = phenoxyacetamido.

Table II
^{1}H NMR Data of Cepham Derivatives

Compd No.[a]	R[b]	X	3α-CH_3	CH_2S	4-H	6-H	7-H
3a	Ft	Cl	1.75	3.06, 3.44 (14.5)	4.95	5.40 (4.5)	5.61 (4.5)
3a	Ft	OH	1.35	2.54, 3.51 (14)	4.58	5.46 (4.5)	5.60 (4.5)
3a	Ft	OAc	1.60	3.32, 3.63 (14.5)	4.95	5.40 (4.5)	5.57 (4.5)
3a	Ft	NO_3	1.73	3.42	5.10	5.42 (4.5)	5.60 (4.5)
3b	Ft	OH	1.28	3.33	4.51	5.36 (4.5)	5.79 (4.5)
3b	V	Cl	1.67	2.75, 3.66 (14)	4.83	5.4 (4.5)	5.67, 5.83
3b	V	Br	1.85	2.75, 3.55 (14)	4.94	5.36 (4.5)	5.66, 5.79
3c	Ft	Cl	1.62	2.98, 3.41 (14)	4.93	5.37 (4.5)	5.58 (4.5)
3c	Ft	OH	1.28	2.48, 3.5 (14)	4.58	5.45 (4.5)	5.60 (4.5)
3c	Ft	OAc	1.61	2.98, 3.42 (14)	4.92	5.39 (4.5)	5.60 (4.5)
3c	Ft	NO_3	1.58	3.39	5.11	5.43 (4.5)	5.60 (4.5)
4a	Ft		2.33	2.85, 3.74 (15)		5.11 (4.5)	5.73 (4.5)
4b	Ft		2.35	3.00, 3.76 (15)		5.13 (4.5)	5.75 (4.5)
4b	V		2.17	3.20, 3.57 (18)		5.02 (4.5)	5.78, 5.92
4c	Ft		2.30	3.02, 3.70 (16)		5.12 (4.5)	5.75 (4.5)

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I.

Table III
^{13}C Chemical Shifts[a] in Penam Systems

	R[b]	R_1[b]	X	2	CH_3(2)	CH_2X(2)	3	5	6	7	$COOR_1$(4)	R(CO)	Σ[c]
1	Ft	CH_3	H	65.8	27.9	31.0	70.8	66.9	58.5	168.3	166.4	166.4	196.0
1	V	CH_3	H	64.0	26.2	31.3	69.7	67.2	57.6	167.3	167.1	172.3	194.5
1	Ft	CH_3	Cl	70.7	23.0	52.9	65.3	67.6	59.7	167.7	166.5	166.4	192.6
1	V	pNB	Cl	69.1	22.1	52.6	65.0	67.0	59.6	167.9	166.5	171.3	191.6
1	Ft	CH_3	NO_3	67.0	22.4	77.1	65.4	67.4	59.6	167.2	166.5	166.7	192.4
2	Ft	CH_3	Cl	70.5	27.5	51.4	68.9	67.2	58.8	167.8	166.4	167.8	194.9
2	Ft	CH_3	NO_3	66.9	25.6	75.6	68.8	67.3	58.4	167.9	166.4	168.1	194.5

[a] In parts per million downfield from internal Me_4Si. All spectra were run in deuteriochloroform solution. [b] Representative spectra of R and R_1 groups follow: Ft: C(1, 2), 131.3; C(3, 6), 123.8; C(4, 5), 134.5. OCH_3: 52.5. pNB: CH_2, 68.1; Ar(1), 141.4; Ar(2, 6), 128.9; Ar(3, 5), 123.7; Ar(4), 147.9; V: CH_2, 66.0; Ar(1), 156.5; Ar(2, 6), 114.7; Ar(3, 5), 129.6; Ar(4), 122.3. pMB: CH_2, 67.5; Ar(1), 142.0; Ar(2, 6), 130.5; Ar(3, 5), 114.0; Ar(4), 159.8; OCH_3, 55.3. [c] The values in this column represent the sums of the C(3), C(5), and C(6) chemical shifts.

and thiazine rings can be used to distinguish between penam and cepham systems.

In some cases specific assignment of the methine resonances is difficult or ambiguous. In such instances the sums of the methine chemical shifts are useful. The last columns of Tables III and IV present these sums for penam and cepham systems. When the substituents R, R_1, and X are equivalent, this sum is about 20 ppm further toward lower field in the penam than in the cepham system. When chemical shifts are measured relative to internal tetramethylsilane, this sum rarely exceeds 175 ppm for compounds of structure **3**.

After having initially distinguished penams **1** and **2** from the cepham **3** by ^{13}C NMR spectroscopy, we noted a generality in the ^{1}H NMR spectra of these compounds which can be used more conveniently for this purpose. Thus, the gem-

Table IV
^{13}C Chemical Shifts[a] in Cepham and Cephem Systems

	R[b]	R_1[b]	X	C(2)	C(3)	C(3')	C(4)	C(6)	C(7)	C(8)	$COOR_1$(4)	R(CO)	D[d]
3	Ft	CH_3	OH	35.3	64.4	24.7	60.8	53.4	58.6	167.3	168.5	161.6	172.8
3	Ft	pMB	OH	35.2	64.4	24.6	60.8	53.2	58.5	167.2	167.6	161.5	172.5
3	Ft	CH_3	ONO_2	31.2	80.7	21.2	55.7	54.2	58.7	167.1	166.4	161.8	168.6
3	Ft	pMB	Cl	37.5	61.7	28.7	61.3	54.0	58.8	167.0	c	161.6	174.1
4	Ft	CH_3		31.5	123.6	20.0	145.5	59.2	59.2	166.5	162.1	160.9	
4	V	pNB		30.3	121.9	20.1	142.5	56.9	58.3	168.7	164.1	161.4	

[a] In parts per million from internal Me_4Si. [b] See footnote *b*, Table III, for representative spectra of the R and R_1 fragments. [c] Not observed. [d] The values in this column represent the sums of the C(4), C(6), and C(7) chemical shifts for structural type **3**.

inal coupling constants observed for the methylene protons in **1** and **2** are consistently in the range of 11.5–12.0 Hz; this coupling in compounds **3** is larger, ranging from 14.0 to 14.5 Hz. In cases wherein this coupling constant can be measured, this criterion should be most useful in distinguishing penams from cephams.

Inspection of Tables III and IV shows that the chemical shifts of carbons throughout these molecules are dependent to varying extents upon the identity of X. In some cases these differences can be explained in terms of the β and γ effects of the substituents.[7] In structure **1**, for example, the chemical shift of carbon 3 shows increasing shielding as X progresses through the sequence H, Br, and Cl. Such a result is consistent with the γ effects of these substituents.[7] Other carbon chemical shift changes are more difficult to explain. Thus the resonance of carbon 6 of **2** appears about 1 ppm toward higher field from that of carbon 6 in **1**, even though the C(5) resonances of the two structures are virtually identical. When both isomers (**1** and **2**) are available, this difference in the C(6) chemical shift may in fact be used to distinguish configurations in these penam systems.

A much more convenient way of distinguishing between structures **1** and **2**, however, depends upon the chemical shift of the methyl protons in these systems. The data in Table I show that the chemical shifts of the protons of 2β-methyl groups are at uniformly lower field than those of the epimeric 2α analogs. Also useful in differentiating between **1** and **2** is the observation that the chemical shifts of the azetidinone protons at positions 5 and 6 are consistently more similar in **2**. In fact these resonances generally occur as two-proton singlets at 60 MHz. More rigorous assignment of configuration in these penam systems can be obtained from measurement of the nuclear Overhauser enhancements.[9]

Through judicious use of ^{13}C and ^{1}H NMR data, therefore, it is easily possible to distinguish between structures **1–4**. Continuing studies are directed toward efforts to use these data to elucidate conformations in these systems.

The structure and stereochemistry of **1** (R = Ft; R_1 = CH_3; X = Cl) were also confirmed by X-ray diffraction methods. Crystals appearing as colorless needles were grown from a mixture of methylene chloride and diethyl ether. The space group is $P2_1$, with two molecules in the unit cell having the dimensions a = 11.246 ± 0.002 Å, b = 7.003 ± 0.002 Å, c = 12.773 ± 0.002 Å, and β = 99.58 ± 0.01°. The intensities of 2019 independent nonzero reflections were measured on a Syntex $P2_1$ automated diffractometer using monochromated copper radiation.

The positions of the sulfur and chlorine atoms were located from a $E^2 - 1$ map. An E map calculated using the phases of the sulfur and chlorine atoms showed the positions of the remaining nonhydrogen atoms. Refinement by the least-squares method, using anisotropic temperature factors, brought the R factor down to 0.115. A difference electron density map calculated at this point revealed an unresolved column of electron density, probably due to a disordering of solvent molecules. Attempts to account for the solvent in further least-squares refinements were unsuccessful. Final refinement was done without including the disordered solvent and converged at a R factor of 0.113. The conformation of the molecule is shown in Figure 1.

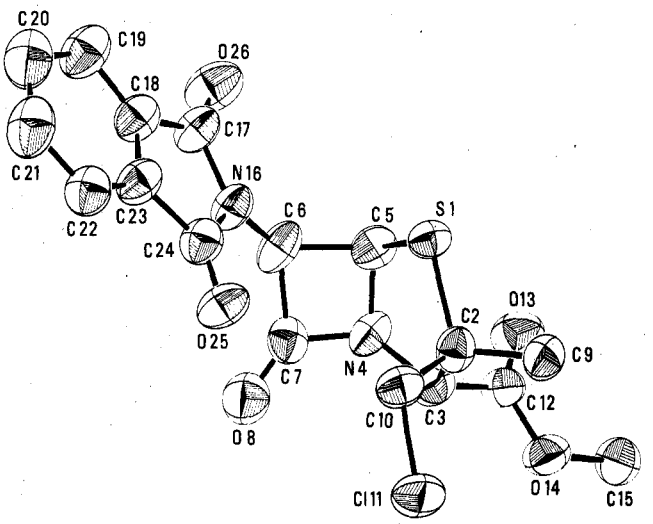

Figure 1. Skeletal conformation of methyl 6β-phthalimido-2β-chloromethyl-2α-methylpenam-3α-carboxylate (**1**) in the crystalline state. Thermal ellipsoids are drawn to include 50% probability.

Experimental Section

The preparation of the compounds studied has been previously described.[2] Carbon-13 NMR spectra were measured in deuteriochloroform solution using concentrations ranging from 0.2 to 0.5 *M*. Initial spectra were recorded at 15.1 or 25.2 MHz at Indiana University, Bloomington, Ind. Subsequent spectra were measured on a Jeol PS-100 Fourier transform spectrometer operating at 25.15 MHz. NMR spectra were recorded using Varian T-60 and HA-100 spectrometers in $CDCl_3$ with Me_4Si as internal reference.

Registry No.—**1a** (R = Et; X = Cl), 51415-59-9; **1a** (R = Et; X = OAc), 39269-09-5; **1a** (R = Et; X = NO_3), 51815-60-2; **1a** (R = Et; X = H), 19788-65-9; **1a** (R = V; X = H), 2315-05-1; **1b** (R = Ft; X = Br), 55450-53-8; **1b** (R = V; X = Cl), 51415-43-1; **2a** (R = Ft; X = Cl), 39067-79-3; **2a** (R = Ft; X = OAc), 55450-54-9; **2a** (R = Ft; X = NO_3), 55450-55-0; **2b** (R = Ft; X = Cl), 51815-65-7; **2b** (R = Ft; X = Br), 55520-58-6; **2b** (R = V; X = Cl), 55450-56-1; **2c** (R = Ft; X = Cl), 52353-29-4; **2c** (R = Ft; X = NO_3), 51815-58-8; **3a** (R = Ft; X = Cl), 40146-21-2; **3a** (R = Ft; X = OH), 51815-69-1; **3a** (R = Ft; X = OAc), 55450-57-2; **3a** (R = Ft; X = NO_3), 55450-58-3; **3b** (R = Ft; X = OH), 55450-59-4; **3b** (R = V; X = Cl), 51546-66-8; **3b** (R = V; X = Br), 55450-60-7; **3c** (R = Ft; X = Cl), 51815-67-9; **3c** (R = Ft; X = OH), 55450-61-8; **3c** (R = Ft; X = OAc), 55450-62-9; **3c** (R = Ft; X = NO_3), 55450-63-0; **4a** (R = Ft), 38584-05-3; **4b** (R = Ft), 51415-20-4; **4b** (R = V), 28974-31-4; **4c** (R = Ft), 51815-59-9.

Supplementary Material Available. Tables of fractional coordinates and anisotropic thermal parameters will appear following

these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C., 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2388.

References and Notes

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Conformations of the Radical Anions from Dialkyl Maleates and Fumarates

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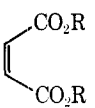
Both dialkyl maleates and fumarates give the same mixture of monoanion radicals, as several workers have noted. It is proposed that all the conformations observed are trans at the original carbon–carbon double bond, and that syn and anti alkyl conformations are observed with primary alkyl groups. This proposal requires that surprisingly slow carbonyl carbon–alkoxyl oxygen rotation occurs in the radical anions.

Electrolytic reduction of dialkyl maleate (1) and fumarate (2) esters in DMSO produces the same mixture of radical anion ESR spectra, indicating that cis–trans isomerization occurs rapidly in the radical anions.[1] Our attribution of the two isomers of $(1,2)\cdot^-$ which we observed to the trans



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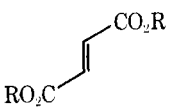

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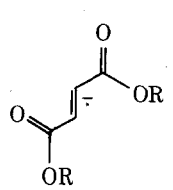
and cis radical anions was incorrect, as the simple fact that we saw substantial amounts of both isomers should have told us; the cis isomer is far more sterically hindered than the trans one, and both of the reported isomers must be trans.[2] The ESR spectra[3] and electrochemistry[4] of these and similar compounds were studied in DMF by Il'yasov and coworkers, and Bard and coworkers have greatly extended such studies.[5] Kemp and coworkers[6] have studied the ESR spectra of these radical anions in liquid ammonia using solvated electrons for generation, and were able to discern no less than four dimethyl maleate–fumarate radical anions. They point out that the two major components A and B (see Table I), which correspond to the species we reported in DMSO, are accompanied by minor components C and D, which have significantly larger g factors. Diethyl fumarate–maleate behaved in a similar manner except that only one minor component was discerned. They attributed the major components A and B to conformations of the fumarate radical anion **3** and **4**, and the minor components C and D to the maleate anions **5** and **6**, stating that **7** was not observed because it would have inequivalent vinyl splittings, whereas A–D were observed to have equivalent ones. They also said additional components cannot be ruled out of these complex spectra, which show many overlapping lines. The remaining symmetrical trans form **8** is also a possibility for A or B.



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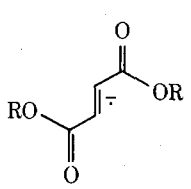

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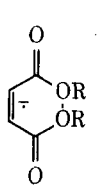

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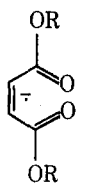

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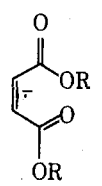

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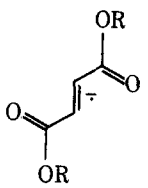

8

In the earlier work, we also reported that a second type of species was generated at higher potential and longer electrolysis times, and attributed it to the anion radical of monoalkyl maleate–fumarate anion.[1] Il'yasov and coworkers[3] stated disbelief in this assignment, and wish to attribute the species to oligomers of some sort, for which they give a couple of structures.

In hopes of discovering more about the isomers of the maleate–fumarate radical anion conformations, we have done additional ESR work on these systems.

Results and Discussion

The radical anions from dimethyl and diethyl fumarate–maleate give complex spectra which are not very long lived in DMSO, and we had significantly less resolution then Kemp and coworkers.[6] The minor conformations they report in ammonia are quite probably also present in DMSO. Since alkyl can be on either of the two types of oxygen present, which we will refer to as "inner" and "outer", there are three dialkyl fumarate conformations (the oi and io conformers being identical when the alkyl groups are the same). If all were of equal energy, one would observe a 1:2:1 mixture of oo, oi, and ii conformations, and the oi confor-