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STRUCTURE AND STEREOCHEMISTRY OF 2-CHLOROMETHYLPENAM AND 3-CHLOROCEPHAM DERIVATIVES STUDIED BY ^{13}C AND ^{1}H NMR SPECTROSCOPY

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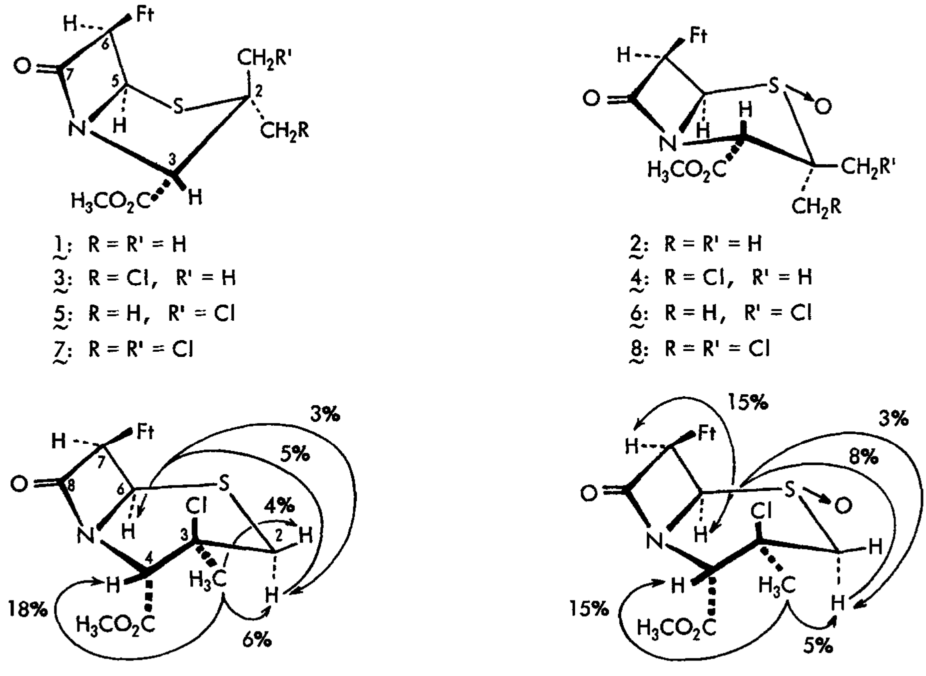
During our investigation of conversion from penicillins to cephalosporins, we needed to assign three isomeric products, obtained from the reaction in the preceding paper,[1] to the four possible structures, e.g., 2α- (3) and 2β-chloro-substituted methyl phthalimidopenicillanates (5), and 3β- (9) and 3α-chloro-7β-phthalimidocephams (11). This problem has become important since previous workers[2] seemed to assign incorrectly the 3-chlorocepham to 5; at an earlier stage the structure and stereochemistry of these isomers could not unambiguously be established readily by ^{1}H NMR as well as other spectroscopies. Thus, we wish to report here our structural assessment of these compounds by ^{13}C and ^{1}H NMR spectroscopy.

The natural-abundance ^{13}C FT NMR spectra of methyl phthalimidopenicillanate (1), 3, 5, 2α,2β-dichloro-substituted derivative (7), 9, and their (R)-sulfoxides (2, 4, 6, 8, and 10) were examined in $CDCl_3$ with ^{1}H noise-decoupling and single-frequency off-resonance decoupling (SFORD)[3] techniques. The ^{13}C signals were assigned according to Archer, et al.[4] and by chemical-shift comparison from compound to compound. The results are listed in TABLE 1.

Differentiation of cepham 9 (or 11) from penams 3 and 5 was straightforward; a triplet signal at δ_C 37.4 in the SFORD spectrum of 9 (or 11) was easily assigned to C-2, whereas CH_2Cl signals of 3 and 5 were found at much lower fields (δ_C 51.6 and 52.9, respectively). Assignments of 3 and 5 were based on the CH_3 signal positions; the 2α-CH_3 signal is known to appear at a field higher than the 2β-CH_3 signal is.[4,5] Thus the CH_3 signal in 3 appears at δ_C 27.6 and that in 5 at 23.0.

With the transformation of the penicillins into their sulfoxides, the CH_2Cl signals were shifted upfield by -9.0 (3→4) and -4.2 ppm (5→6) and the CH_3 signals by -4.8 (3→4) and -8.8 ppm (5→6). Since in



1: R = R' = H
3: R = Cl, R' = H
5: R = H, R' = Cl
7: R = R' = Cl

2: R = R' = H
4: R = Cl, R' = H
6: R = H, R' = Cl
8: R = R' = Cl

9 (11: 3α-Cl, 3β-CH$_3$)

10 (12: 3α-Cl, 3β-CH$_3$)

FIGURE. Structure and conformation (Ft = phthalimido).

penicillins the shielding is known to be greater for 2α-CH$_3$ than for 2β-CH$_3$[5] (steric γ-effects),[3] the above finding indicates that the CH$_2$Cl-carbons locate at the γ-positions from the S-atoms, and also that the CH$_2$Cl in 3 is in the α-side. In a change from cepham 9 (or 11) into 10 (or 12), the C-2 (β from S) and 3-CH$_3$ (δ from S) signals are both deshielded by +21.6 and +0.8 ppm, respectively.

The γ-effects of (R)-sulfoxidation in the penams were found to be stronger upon 2α-CH$_2$R (-7~-12 ppm) than 2β-CH$_2$R (-4~-6 ppm), as observed previously.[4,5] This fact results from a conformational change from sulfide to sulfoxide;[4,5] all penams under study were also subjected to examinations by nuclear Overhauser effects[6] (NOE) in ^{1}H NMR to show conformational changes similar to those reported,[5] as indicated in the FIGURE.[7]

Chlorination effects in the penams exhibited a different trend between the sulfides and the (R)-sulfoxides; this can result also from their conformational difference. It should be noted that chlorination at 2α-CH$_3$ little shields C-3 in the sulfoxides, and that C-5 is more deshielded by chlorination at 2β-CH$_3$ (+3.1 ppm)

TABLE 1. ^{13}C Chemical Shift Data, δ_C[a]

Carbon No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Carbon No.	**9**	**10**
2	65.9	71.6	70.8	75.3	70.8	78.6	75.8	83.0	2	37.4	59.2
3	70.9	65.9	67.3	64.8	65.5	63.4	64.4	62.6	3	61.6	66.1
5	67.0	81.0	69.2	82.8	67.8	84.1	67.2	86.7	4	61.2	59.6
6	58.6	55.5	59.0	55.8	59.8	56.5	60.1	56.5	6	53.9	74.6
7	168.5[b]	168.2[b]	168.1	167.7	168.0[b]	167.6[b]	167.1[b]	166.5[b]	7	59.0	57.9
2α-CH_2R	27.9	16.3	51.6	42.6	23.0	14.2	46.8	39.9	8	161.6[b]	160.7[b]
3β-CH_2R	30.9	25.0	27.6	22.8	52.9	48.7	48.1	45.2	3-CH_3	28.6	29.4
$CO_2\underline{C}H_3$	52.4	52.9	52.9	53.3	52.6	53.5	53.0	53.3	$CO_2\underline{C}H_3$	52.8	53.1
$\underline{C}O_2CH_3$	168.3[b]	167.2[b]	168.1	167.7	166.8[b]	165.8[b]	166.5[b]	165.4[b]	$\underline{C}O_2CH_3$	167.5[b]	166.1[b]

[a] ^{13}C FT NMR spectra were determined with a Varian NV-14 FT NMR spectrometer operating at 15.09 MHz at 30° using $CDCl_3$ solutions containing TMS as an internal reference (δ_C 0) in 8-mm tubes; precisions of δ_C are ±0.1. δ_C values for the phthalimido group were as follows: 166.7 ± 0.1 (CO), 124.0 ± 0.2 (4'-C), 134.8 ± 0.3 (5'-C), and 131.5 ± 0.2 (8'-C). [b] These assignments are tentative.

than by that at 2α-CH_3 (+1.8 ppm) in the sulfoxides, whereas an opposite trend is seen in the sulfides.

As a result, the above ^{13}C NMR spectral evidence has established the structure and stereochemistry of penams **3** and **5**.

^1H NMR spectroscopy was also useful for diagnosing the structures of the (R)-sulfoxides, as has been known.[5] As shown in TABLE 2, aromatic solvent induced shifts (ASIS)[8] with C_6D_6 were pronounced for 2β-CH_2R (or 2β-H) more than for 2α-CH_2R (or 2α-H).[5,9] The difference between the ASIS values for 2α-H and 2β-H in cepham **10** (or **12**) is clearly larger than those between the geminal CH_2Cl protons in penams **4** and **6** are. Furthermore, lanthanide-induced shifts[10] with $Eu(dpm)_3$ in $CDCl_3$ for these sulfoxides exhibited clear large differences between 2α-CH_2R (or 2α-H) and 2β-CH_2R (or 2β-H), the values for the former being considerably larger as reported[11] (see TABLE 2). These results are in harmony with those from ^{13}C NMR, confirming that these sulfoxides have the (R)-configuration, simultaneously.

Finally, both configuration at C-3 and conformation of the 3-chlorocepham and its (R)-sulfoxide were simultaneously revealed by NOE measurements[6] to be **9** and **10**, respectively, among four possible stereostructures[5] expected for each compound. The results are indicated in the FIGURE, in which the only positive NOE enhancements are represented by percentage increases in signal intensities; the measurements were carried out between all measurable pairs of proton signals. As a conclusion, the structures of all compounds examined have been established, unequivocally.

TABLE 2. ^{1}H NMR Spectral Data on the Sulfoxides Examined[a]

Compound	b	3β-H	5α-H	6α-H	2α-CH_2R		2β-CH_2R		CO_2CH_3
	δ[c]	4.62	4.84	5.88	1.33		1.82		3.85
2	Δδ[d]	-0.03	-0.33	-0.36	-0.16		-0.31		-0.54
	ΔEu	4.59	11.7	3.56	7.42		3.11		1.32
	δ	4.68	5.17	5.90	3.90	4.04	1.94		3.85
4	Δδ	-0.10	-0.29	-0.39	-0.17	-0.14	-0.31		-0.45
	ΔEu	3.68	9.41	2.86	5.86	6.85	2.42		0.94
	δ	4.94	4.98	5.95	1.43		4.14		3.85
6	Δδ	-0.03	-0.29	-0.41	-0.15		-0.25		-0.54
	ΔEu	3.37	7.95	3.61	5.12		2.18	2.68	0.77
	δ	4.93	5.18	6.00	3.98	4.13	4.35	4.47	3.87
8	Δδ	-0.02	-0.21	-0.36	-0.01	-0.01	-0.10	-0.05	-0.54
	ΔEu[e]	4.1	9.3	3.5	6.6	7.3	3.7	4.0	0.65
		4β-H	6α-H	7α-H	2α-H	2β-H	3-CH_3		CO_2CH_3
	δ	4.76	5.12	5.93	3.53	3.74	1.78		3.85
10	Δδ[f]	-0.11	-0.19	-0.30	-0.20	-0.41	-0.41		-0.41
	ΔEu	3.19	14.0	5.71	8.75	3.42	1.64		1.07

[a] ^{1}H NMR spectra were taken with a Varian A-60A spectrometer in $CDCl_3$ and C_6D_6 at 38°; precisions of δ_H are ±0.02. NOE experiments were carried out on a Varian HA-100 spectrometer operating at 100 MHz in the frequency-swept and TMS-locked mode in $CDCl_3$; accuracies are ±2%. For the data on the sulfides and a simple procedure proposed for diagnosing their structure, see the preceding paper.[1] [b] δ, Δδ, and ΔEu are ^{1}H chemical shift, ASIS with $C_6D_6 = \delta_H(C_6D_6) - \delta_H(CDCl_3)$, and $Eu(dpm)_3$-induced shift at a 1 : 1 molar ratio of Eu/substrate in each shift curve, respectively; a plus sign represents a downfield shift. [c] Identical with the reported values.[9] [d] Considerably differ from the reported values.[9] [e] Extrapolated values because of the sample decomposition during additions of $Eu(dpm)_3$. [f] Using a 1 : 1 mixture of C_6D_6 and $CDCl_3$ because of low solubility in C_6D_6.

REFERENCES

(1) H. Tanida, T. Tsuji, T. Tsushima, H. Ishitobi, T. Irie, T. Yano, H. Matsumura and K. Tori, the preceding paper.

(2) S. Kukolja and S. R. Lammert, J. Amer. Chem. Soc. 94, 7169 (1972).

(3) G. C. Levy and G. L. Nelson, "Carbon -13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York (1972).

(4) R. A. Archer, R. D. G. Cooper, P. V. Demarco and L. F. Johnson, Chem. Commun. 1291 (1970).

(5) P. V. Demarco and R. Nagarajan, "Cephalosporins and Penicillins. Chemistry and Biology," Ed. E. H. Flynn, Chapter 8, Academic Press, New York (1972).

(6) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect. Chemical Applications," Academic Press, New York (1971).

(7) K. Tori, T. Tsushima and H. Tanida, unpublished results.

(8) For a leading reference, see K. Tori, I. Horibe, H. Shigemoto and K. Umemoto, Tetrahedron Lett, 2199 (1975).

(9) R. D. G. Cooper, P. V. Demarco and D. O. Spry, J. Amer. Chem. Soc. **91**, 1528 (1969).

(10) For a review, see B. C. Mayo, Chem. Soc. Rev. **2**, 49 (1973).

(11) A. K. Bose, B. Dayal, H. P. S. Chawla and M. S. Manhas, Tetrahedron Lett. 3599 (1972).