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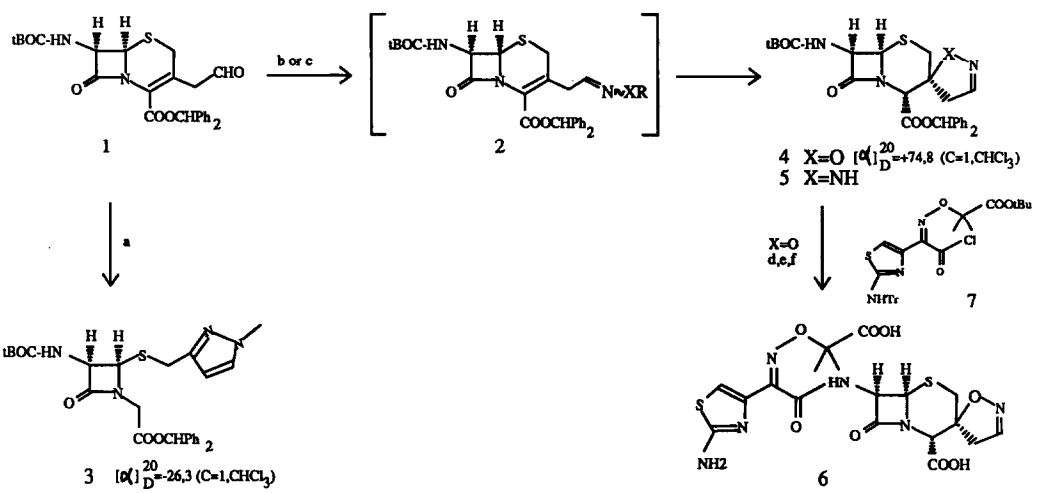
SYNTHESIS AND STRUCTURE ELUCIDATION OF NEW SPIROCEPHAMS

P. Bruneau, L.F. Hennequin*, L. Quéré, M.C. Scherrmann, P.J. Siret
I.C.I. PHARMA, Centre de Recherches, Zone Industrielle La Pompelle,
B.P. 401, 51100 REIMS (FRANCE)

Abstract : Spirocephams 4 and 5 have been obtained from aldehyde 1 and hydroxylamine or hydrazine, as single diastereoisomers. Structures of these compounds have been elucidated by NMR experiments and MNDO calculations.

In the course of a programme to design cephems modified at the 3 position, we condensed aldehyde 1(1) with hydroxylamine and hydrazine and obtained spirocephams 4 and 5 respectively as single diastereoisomers(2).

SCHEME 1



1 2 4 X=O $[\alpha]_D^{20}$=+74,8 (C=1,$CHCl_3$) 5 X=NH 7

3 $[\alpha]_D^{20}$=-26,3 (C=1,$CHCl_3$) 6

a) $MeNH-NH_2$ (1.1 eq.) / EtOH / 0°C / 2 hrs / 40 % ; b) NH_2OH, HCl (1.5 eq.) / pyridine (1.5 eq.) / EtOH / 60°C / 2 hrs / 40 % ; c) NH_2-NH_2 (1 eq.) / EtOH / 0°C / 2 hrs / 45 % ; d) TSOH / CH_3CN / 90 % ; e) 7 / CH_2Cl_2 / Et_3N / 35 % ; f) TFA / H_2O / 26 %

This result can be explained by the formation of intermediates 2 which react further by 1-4 addition to the Michael acceptor present in the 6-membered ring to give the spiro-annelated products. In the case of methylhydrazine, the intermediate spirocepham has not been isolated ; reaction goes directly to azetidinone 3(2) resulting from opening of the six-membered ring.

Formation of such 3-spirocephams has been reported from 3-acetoxymethyl cephalosporins and bidentates(3,4) ; during a base catalysed rearrangement of cyclohexenopyridinio cephalosporins(5) and during basic cleavage of 3-thiazoliomethyl cephalosporins(6).

The spirocyclisation step leads to only one isomer in which two new chiral centers are created. Thus, we were interested in determining the exact configurations of C3 and C4. This has been achieved by using spectroscopic(7), molecular mechanics methods (MMP2)(8,9) and semi-empirical molecular orbital methods (MNDO)(10) and (AMPAC)(11). Both compounds (4 and 5) gave similar results and can therefore be considered to have the same stereochemistry.

Important features of the ^1H spectra (Table 1) include (see Scheme 2) : 1) an AB pattern for the methylene group at C2 and C9 with a further small splitting on H9 and H9' in 5 (X = NH) due to coupling with H10 ; since this coupling is not observed in compound 4 (X = O) unambiguous assignments for H2H2' and H9H9' are provided by comparison of the geminal coupling constants for each methylene group in the two compounds ; 2) H4 can readily be identified as a singlet ; 3) H6 and H7 exhibit the usual β-lactam chemical shifts and coupling constants(12) ; 4) ^1H spin decoupling experiments showed that H4 and H2' present a long range coupling constant which can be explained by a H4C4C3C2H2' W conformation.

TABLE 1: ^1H Chemical shifts of compounds 4 and 5 (δ ppm, J Hz)

SIGNAL	4		5	
	$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6
H2	3.28 d AB (J = 14.0)	2.91	3.20 d AB (J = 13.9)	3.00
H2'	2.67 d AB (J = 14.0)	2.09	2.56 d AB (J = 13.9)	2.03
H4	4.80 s	4.74	4.87 s	5.20
H6	5.13 d (J = 4.6)	4.89	5.17 d (J = 4.6)	4.93
H7	5.38 dd (J = 10.4 ; 4.6)	5.34	5.31 dd (J = 9.2 ; 4.6)	5.22
NH	5.67 d (J = 10.4)	5.52	5.29 d (J = 9.2)	6.58
H9	2.96 d AB (J = 18.0)	2.31	2.73 dd (J = 17.6 ; 1.3)	2.38
H9'	2.57 d AB (J = 18.0)	1.80	2.19 dd (J = 17.6 ; 1.3)	1.70
H10	7.11 s	6.28	6.70 bs	6.20
$CHPh_2$	6.95 s	6.86	6.94 s	6.91
Ph_2	7.37 m	7.10	7.35 m	7.2

Further NOE experiments were performed (Table 3). The most significant data are : 1) enhancements observed from H2 to H6, H9' to H2 and H2' and H4 to H9. Since H6 is in an α orientation, H2 must also be α ; for H9' the small enhancement to both H2 and H2' suggest that this proton bisects the H2 C2 H2' plan. This can only arise when the C9 methylene group is in the same α orientation as H2 ; 2) A NOE effect observed from H4 to H9 and no enhancement observed to any other proton led to the hypothesis that H4 is β. This result is in agreement with a previous report in the literature(13). Model examination indicates that if H4 were in the α orientation, then a NOE might be observed to H2 and/or H6(13). To confirm this H4 β assignment further experiments were initiated (two dimensional NOESY, irradiating at H4 and observing the carbon spectrum) but gave no additional evidence.

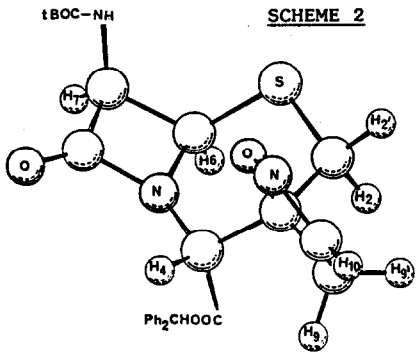
Thus molecular mechanics and MNDO calculations were performed on intermediate 4 (Table 2). For such dihydrocephalosporins, four possible conformations (two chairs and two boats) are conceivable, which, after minimisation using MMP2(9) converged towards the two most stable structures : twist T1 and chair C1(14) (these results have been confirmed by MNDO calculations). After further minimization of the C4 and C7 side chains in both the C1 and T1 preferred conformations, 16 structures were obtained(15) ; these have been submitted to MNDO semiempirical calculations and led to the αα, αβ, βα and ββ configurations of minimal energy for each form. Results in Table 2 show the eight most stable configurations (four chairs and four twists).

TABLE 2 : 8 Most stable conformations after MDLMM2 and MNDO minimisation

FORM (H4, C9)	E MNDO kcal/mol	(E - E Min) MNDO	FORM (H4, C9)	E MNDO kcal/mol	(E - E Min) MNDO
Chair (β,β)	-119.97	0.0	Twist (β,β)	-118.60	+1.39
Chair (β,α)	-119.97	+0.03	Twist (β,α)	-117.02	+2.97
Chair (α,β)	-115.43	+4.54	Twist (α,β)	-116.61	+3.37
Chair (α,α)	-116.25	+3.72	Twist (α,α)	-117.47	+2.52

NMR results and a literature precedent(13) gave evidence that C12 is α and that H4 is β(16). Calculations also reinforce the proposed assignments, the chair βα (Scheme 2) being the most stable isomer.

SCHEME 2



4 : CHAIR H4β C9α

TABLE 3 : NOE Experiments measured on compound 4 (X = O)(18)

Irradiated proton	Enhanced proton (%) (C_6D_6)	d measured A
H4	H9 (2.1)	H4-H9 : 2.78
H2	H2'(24.6);H9'(1.6)	H4-H10 : 4.29
	H6 (2.5)	H9'-H2': 2.63
H2'	H2 (24.8);H9'(1.9)	H9'-H2 : 2.58
H9	H9'(14.6);H4 (2.9)	H2-H6 : 3.18
	H10(1.2)	H4-H2' : 4.37
H9'	H9(15.5);H10(1.6)	
	H2 (2.3) ; H2'(1.9)	

Thus we can conclude that the only isomer isolated in this spiroannelation reaction is the 3S, 4R spirocepham which corresponds to the thermodynamically most stable one(5). Further chemical transformations have been achieved to obtain the final oximino aminothiazole spirocepham 6(2) (Scheme 1) which is virtually devoid of antibacterial activity.

Acknowledgment : We thank Mr D. GREATBANKS, Mr B. WRIGHT and Dr B. MASEK from ICI Pharmaceuticals for NOE measurements and helpful discussions.

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2) Analyses (^1H, ^{13}C NMR, IR and Mass (FAB+)) (3, 4, 5, 6) and C,H,N analyses (3, 4, 5) are in good agreement with the proposed structures. Compounds 3, 4, 5 are obtained as amorphous solids. 3 : m.p. = 70°C (decomp.) ; 4 : m.p. = 202-204°C ; 5 : m.p. = 120°C (decomp.)

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7) Unambiguous assignment of all ^{1}H and ^{13}C chemical shifts have been achieved from ^{1}H-^{1}H decoupling experiments, ^{1}H decoupled and ^{13}C coupled spectra and ^{13}C-^{1}H correlation experiments and from literature precedent(11,5) - 4 : NMR ^{13}C ($CDCl_3$) : 28.09 (q) ; 30.96 (t, C2) ; 43.47 (t, C9) ; 54.36 (d, C6) ; 56.48 (d, C4); 61.27 (d, C7) ; 76.81 (s, C3) ; 79.10 (d) ; 80.76 (s) ; 126.7 ; 128.7 (3c) ; 138.40 (s) ; 146.11 (d, C10) ; 154.45 (s) ; 165.91 (s) ; 166.14 (s) // 5 : NMR ^{13}C ($CDCl_3$) : 28.12 (q) ; 30.68 (t, C2) ; 42.61 (t, C9) ; 55.63 (d, C6) ; 57.72 (d, C4) ; 59.44 (s, C3) ; 61.16 (d, C7) ; 78.80 (d) ; 80.85 (s) ; 126.7, 128.7 (3c) ; 138.62 (s) ; 142.48 (d, C10) ; 154.58 (s) ; 165.57 (s) ; 166.63 (s)

8) N.L. ALLINGER and V. BURKER, Molecular Mechanics - American Chemical Society, Washington, D.C. (1982)

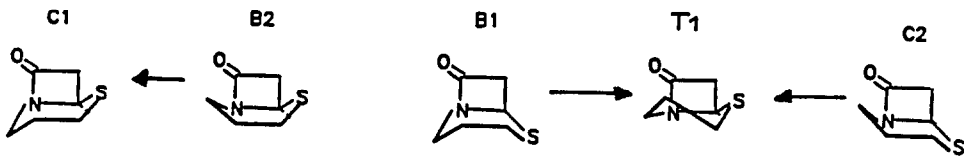
9) MMP2 version 7.0 distributed by Molecular Design Ltd. This program being incompletely parameterized for such a system, the missing parameters have been deduced from X-ray crystallographic data of a 3,4-dihydrocephalosporin (Cambridge crystallographic data base, ref. code : BUYGOR) and an isoxazoline (ref. code : DIHIXL10)

10) M.J.S. DEWAR and W. THIEL, J. Amer. Chem. Soc. 1977, 99, 4899

11) M.J.S. DEWAR and J.P.P. STEWART, Quantum Chem. Prog. Exchange Bull. 1986, 6, 24, QCPE Program 506

12) A.F. CASY, Magnetic Resonance in Chemistry 1986, 24, 465

13) Other workers(5) have observed a NOE to H6 from H4 in similar 3-spiro cephalosporins and on this basis assigned an the α orientation to H4

14) 

15) In the C1 chair, substituents at positions 3 and 4 can be α or β leading to four possible different conformations. For each pair (αα, αβ, ββ, βα) a molecular mechanics conformational analysis has been carried out (torsion varying from 0° to 330° using 30° increments), each side chain being studied separately. Each chain presents two minima which have been used to build the four conformational combinations of the side chain for each of the four different configurations of substituents at C3 and C4, leading to 16 structures in all which were submitted to MNDO calculations

16) This α configuration or axial orientation of the ester group is in agreement with observations made by Cohen on Δ2 cephalosporins(17)

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18) Similar NOE enhancements were obtained with compound 5 (X = NH)

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