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FORMATION OF A NOVEL 3-SPIRO CEPHALOSPORIN BY A BASE CATALYSED REARRANGEMENT

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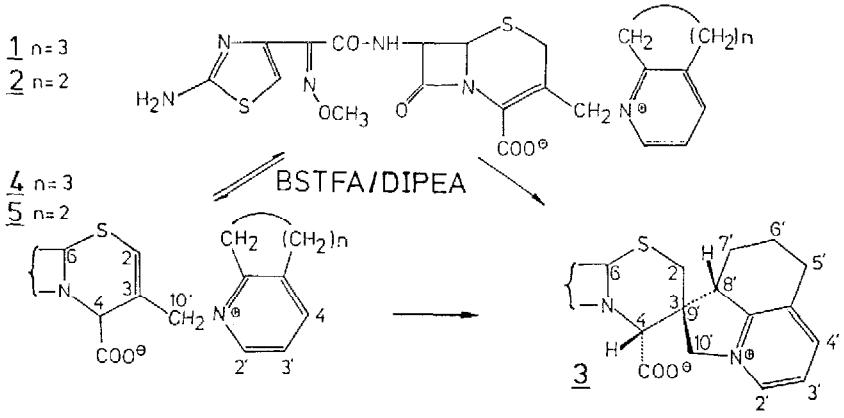
Summary
*The cyclohexenopyridinio cephalosporin **1** (Cefqinome) reacts in the presence of a base irreversibly to the spiro compound **3**. The structure has been elucidated by twodimensional NMR-experiments. The energy of the possible stereoisomers of **3** has been calculated by MNDO.*

Introduction

Several degradation and rearrangement products of cephalosporins have been isolated and identified, most of them being derived from hydrolysis of the β-lactam ring, extrusion of the sidechain and/or isomerization[1]. As is well documented for cephalosporins the Δ3 double bond is apt to rapid isomerization to the Δ2 position[2,3]. The formation of 3-spiro cephalosporins has been reported for 3-acetoxymethyl cephalosporins and bisdentate nucleophiles[3,4].



Results

In the course of our own investigations of the stability of β-lactam antibiotics the cyclohexenopyridinio derivative **1** was treated with the sevenfold excess of bis(trimethylsilyl)trifluoroacetamide (BSTFA) cooled to 15 °C and neutralised with tertiary amines like N'N-diisopropylethylamine. The expected equilibrium between **1** and the Δ 2 isomer **4** is rapidly attained, followed by the irreversible appearance of a novel product **3** . In contrast, similar treatment of the cyclopentenopyridinio compound **2** (Cefpirome) results only in an equilibrium mixture of **2** and its Δ2 isomer **5** in the approximate ratio 1 : 4 .

The compound **3** differed in its spectroscopic properties from the Δ 2 isomer **4**. The proton-NMR spectrum (see fig. 1) lacks additional olefinic resonances but reveals two AX systems, the methylene groups C-2 and C-10'. The COSY spectrum[5] resolved small couplings between a new singlet at

4.23 ppm (signal i) and the signal from H-6 as well as from one of the two H-2 protons. Therefore this signal was assigned as H-4. In addition the ^{13}C-NMR spectrum (see tab. 1) of **3** exhibits a new singlet resonance at 49.6 ppm. The chemical shift is well outside the range for an unsaturated carbon and could be explained by a di-substituted C-3. The substitution becomes clear, when following the connectivities within the aliphatic part of the cyclohexenopyridinio sidechain (see fig. 1).

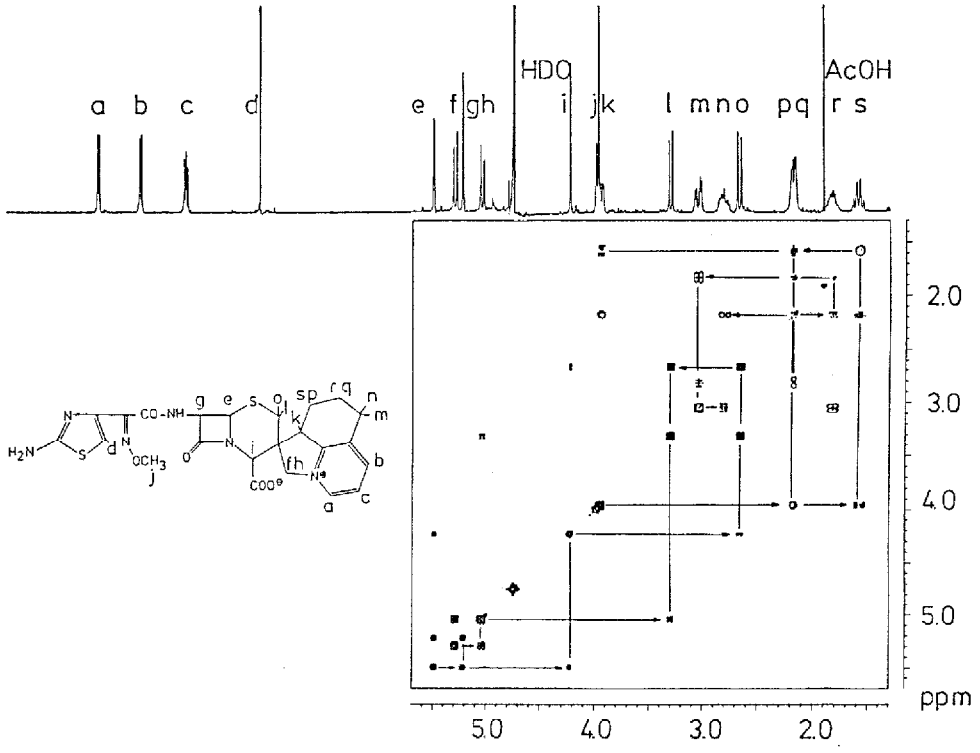


Fig. 1 : ^{1}H-NMR and part of the COSY spectrum of **3** in D_2O.

Starting from the low field methylene group adjacent to the aromatic ring (signals m and n, C-5') the connectivities to the next methylene group (signals r and q, C-6') are unravelled. Following these couplings the next CH_2 group (signals p and s, C- 7') can be assigned. The last signals are only coupled to one additional partner (signal k), which lacks a geminal coupling but reveals one small (long-range) coupling to signal i. It was thus concluded that the C- 8' of the cyclohexenopyridinio sidechain is substituted by a quarternary carbon, namely the C-3 of the cepheme.
The spiro-compound **3** is structurally related to the reaction products of cephalosporins with bisdentate nucleophiles, e.g. mercaptopyridines [4] . In contrast to these examples, however the reaction of **1**, irreversiblyleads to **3** whereas the formation of spiro compounds with bisdentate nucleophiles is reversible in aqueous media in the presence of a base. The spiro compound **3** is nearly devoid of antibacterial activity.

Tab. 1 : ^{1}H- and ^{13}C-chemical shifts of the compounds **1**, **2**, **3**, **4** and **5**

compound	**1**	**2**	**3**			**4**	**5**
solvent	DMSO	DMSO	D_2O		DMSO	DMSO	DMSO
signal				^{13}C mult			
H - 2	3.37	3.41	3.33	27.53 t	3.00	6.22	6.52
H - 2	3.37	3.41	2.70		2.72		
H - 3	-	-	-	49.77 s	-	-	-
H - 4	-	-	4.26	49.68 d	3.72	4.06	4.09
H - 6	5.18	5.19	5.23	62.62 d	4.96	5.32	5.33
H - 7	5.86	5.87	5.51	64.65 d	5.29	5.35	5.42
O-CH_3	3.82	3.81	3.99	65.57 q	3.83	3.82	3.82
Pyridyl 2'	8.72	8.68	8.61	147.76 d	8.78	9.02	8.79
3'	7.93	7.92	7.80	128.80 d	7.83	7.89	7.87
4'	8.36	8.42	8.22	140.64 d	8.24	8.30	8.38
Alkyl 5'	3.05	3.13	3.08	28.86 t	2.99	2.96	3.13
5'	3.05	3.13	2.85		2.72	2.96	3.13
6'	1.87	2.25	2.22	24.92 t	2.10	1.89	2.22
6'	1.87	2.25	1.86		1.73	1.89	2.22
7'	1.75	3.28	2.23	24.62 t	2.12	1.77	3.48
7'	1.74	3.28	1.63		1.61	1.75	3.27
8'	2.97	-	3.99	57.11 d	3.87	3.17	-
8'	2.97	-	-		-	3.02	-
10'	5.84	5.55	5.32	68.68 t	4.58	5.52	5.58
10'	5.47	5.44	5.06		4.44	5.48	5.30

Stereochemical considerations

In order to further elaborate on the structure of **3** NOE difference experiments [6] were carried out. The results gave evidence of the relative configuration of C-3 and C-8' and of the absolute configuration of C-4.

Irradiation of H-4 gave a response in H-2 as well as in one of the two H-10'. Irradiating H-2 as well as the other H-10' gave a response in H-8'. From these constraints the relative configuration at the two stereochemical centres can be modeled as depicted in fig. 3. The configuration must be 3 (R),8'(R) or 3(S),8'(S).

Keeping **3** in aqueous solution yields an equilibrium mixture containing **3** and 4-epi **3** at an approximate ratio of 7 : 3. Irradiating the H-4 signal of the newly formed compound gave an NOE of the H-6 signal. Thus the newly formed isomer is characterized by an α-orientation of H-4 (4(S) configuration). Therefore the original compound **3** must have been 4(R). This configuration has also been reported for the $\Delta 2$ isomers [2,3].

These findings are further substantiated by theoretical calculations. It was assumed that the thiazole-oximino moiety does not effect the stability of the possible isomers. Therefore the structure was simplified by removing the thiazole-oximino group.

Four isomers **c1** through **c4** were modeled and subjected to MNDO calculations. All structural parameters were varied starting from standard values for bond lengths, bond angles and dihedral angles. The calculated heats of formation are given in Tab. 2.

The most stable isomer is **c 2.** It could be formed under thermodynamic control of the reaction. However, the calculated energy difference between **c2** and **c1** indicates that **c2** should not readily interconvert to **c1** . On the other hand, the difference in energy between **c4** and **c3** is sufficiently small to explain the presence of these isomers. We therefore conclude that atoms 3 and 8' are S-configurated.

Tab. 2 : Calculated heats of formation for four different stereoisomers of **3**

Isomer	absolute configuration	heats of formation kcal / mol	Isomer	absolute configuration	heats of formation kcal / mol
c1	3 (R), 4 (S), 8' (R)	- 12.2	**c3**	3 (S), 4 (S), 8' (S)	- 22.6
c2	3 (R), 4 (R), 8' (R)	- 28.2	**c4**	3 (S), 4 (R), 8' (S)	- 24.5

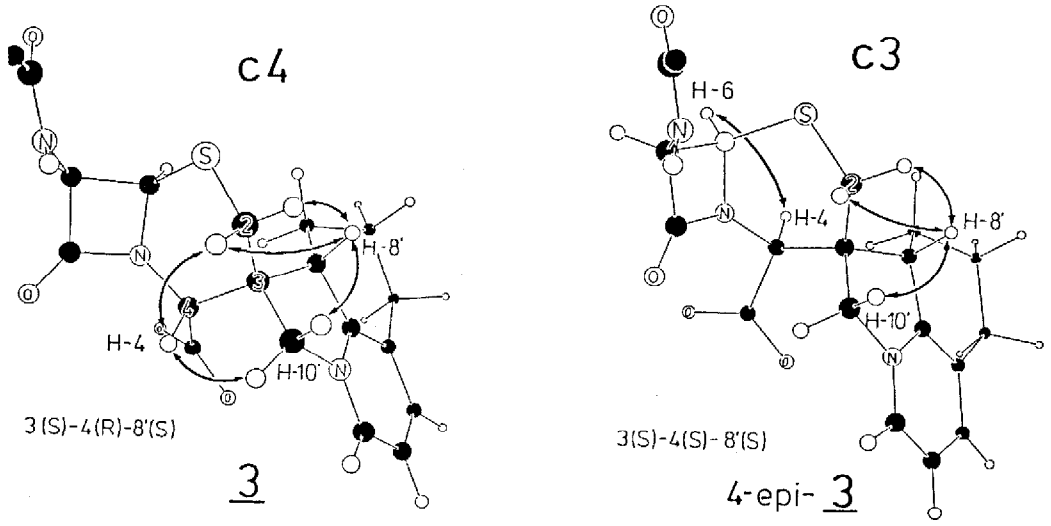


Fig. 2 : Threedimensional structures of **3** and 4-epi **3** . Proton-proton NOEs are indicated by arrows.

Conclusion

In the case of most pyridinio substituted cephalosporin derivatives such as HR 810 the △ 3 → △ 2 conversion is the preferred process whenever nucleophiles act on the cephalosporin in the presence of silylating agents. With **1** the formation of **3** can be rationalized by the base catalyzed abstraction of a proton in the 8'- position of the cyclohexenopyridinio residue followed by the addition of the intermediate carbanion to the activated double bond of the cephem ring.

References and notes

dedicated to Prof. W. Bartmann on the occasion of his 60th birthday

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