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265. New β -Lactam-Antibiotics. Fluorinated Cephalosporins

Preliminary Communication

Modifikationen von Antibiotika. 15. Mitteilung [1]

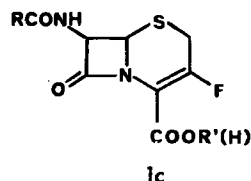
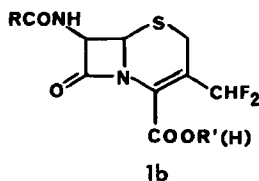
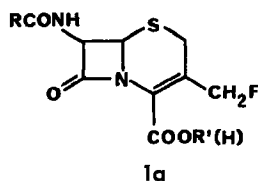
by Beat Müller, Heinrich Peter, Peter Schneider and Hans Bickel

Departement Forschung, Division Pharma, Ciba-Geigy AG, Basel

(9. IX. 75)

Zusammenfassung. Neue Cephalosporine, die in 3-Stellung eine Fluormethylgruppe aufweisen (**9**, **17**/Schema 1), wurden ausgehend von **2b** unter Verwendung von 2-Chlor-1,1,2-trifluor-triäthylamin als Fluorierungsmittel hergestellt. Mit Piperidin-schwefeltrifluorid erhielt man ferner aus **18** die 3-Difluormethyl-cephemverbindung **19** (Schema 2), die nach bekannten Methoden in antibakteriell wirksame Cephalosporine (**20a**, **b**) übergeführt wurde. 3-Fluor-cephemderivate, z.B. **23b**, liessen sich ausgehend von entsprechenden 3-Hydroxy-cephemverbindungen, mit diesem Reagens jedoch nur in sehr geringer Ausbeute herstellen.

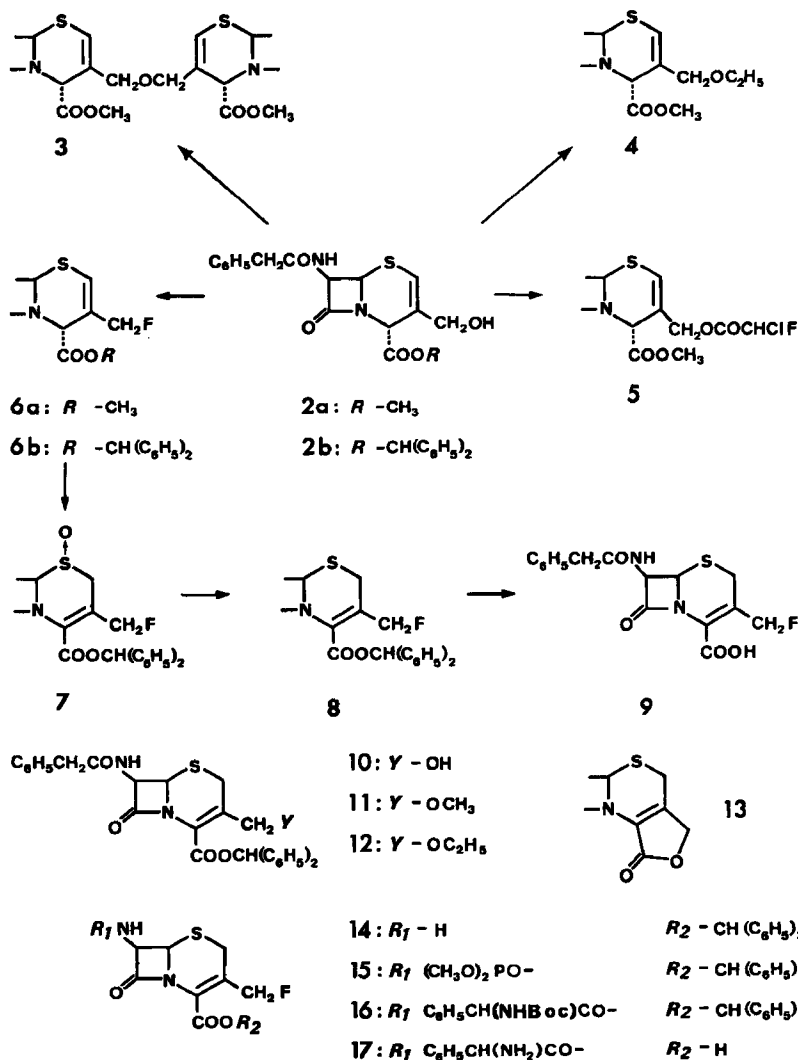
To our knowledge, 3-fluoromethyl-3-cephems (**1a**) and 3-difluoromethyl-3-cephem derivatives **1b** have not yet been described. 3-Fluoro-3-cephem derivatives of type **1c** have recently been disclosed in the patent literature [2].



We now report the preparation of such fluorides utilizing either 2-chloro-1,1,2-trifluoro-triethylamine (CTT) [3] [4] or piperidino sulfur trifluoride (PST) [5] [6] as fluorinating agents.

Addition of 2.0 eq. of CTT to alcohol **2a** (Scheme 1) in CHCl_3 solution at 0° over 30 min and additional stirring for 30 min gave a mixture of two components, which were separated by crystallization and chromatography on silicagel: 1) *Symmetrical ether 3* (26%) [m.p. $206-208^\circ$; UV.¹⁾: 243 (13,500); IR. (nujol): 2.98, 5.62, 5.74, 6.04, 6.52; NMR. ($\text{DMSO}-d_6$): 3.58 (s/ CH_2CO); 3.77 (s/ OCH_3), 4.05/4.06 ($AB/J = 16/\text{CH}_2\text{O}$); 4.90 ($d/J = 1/\text{H}-\text{C}(4)$); 5.22 ($d/J = 4/\text{H}-\text{C}(6)$); 5.64 ($d \times d/J = 4$ and $9/\text{H}-\text{C}(7)$); 6.39 ($d/J = 1/\text{H}-\text{C}(2)$); 7.26 (s/ C_6H_5); 7.50 ($d/J = 9/\text{NHCO}$)]; 2) *3-fluoromethyl- Δ^2 -cephem-ester (6a)* (36%) [m.p. $141-145^\circ$; UV.: 245 (7300); IR. (CH_2Cl_2): 2.90, 5.59, 5.70, 5.91, 6.63; NMR. (CDCl_3): 3.57 (s/ CH_2CO); 3.73 (s/ CH_3O); 4.74 and 4.92 ($ABF/J = 11$,

Scheme 1



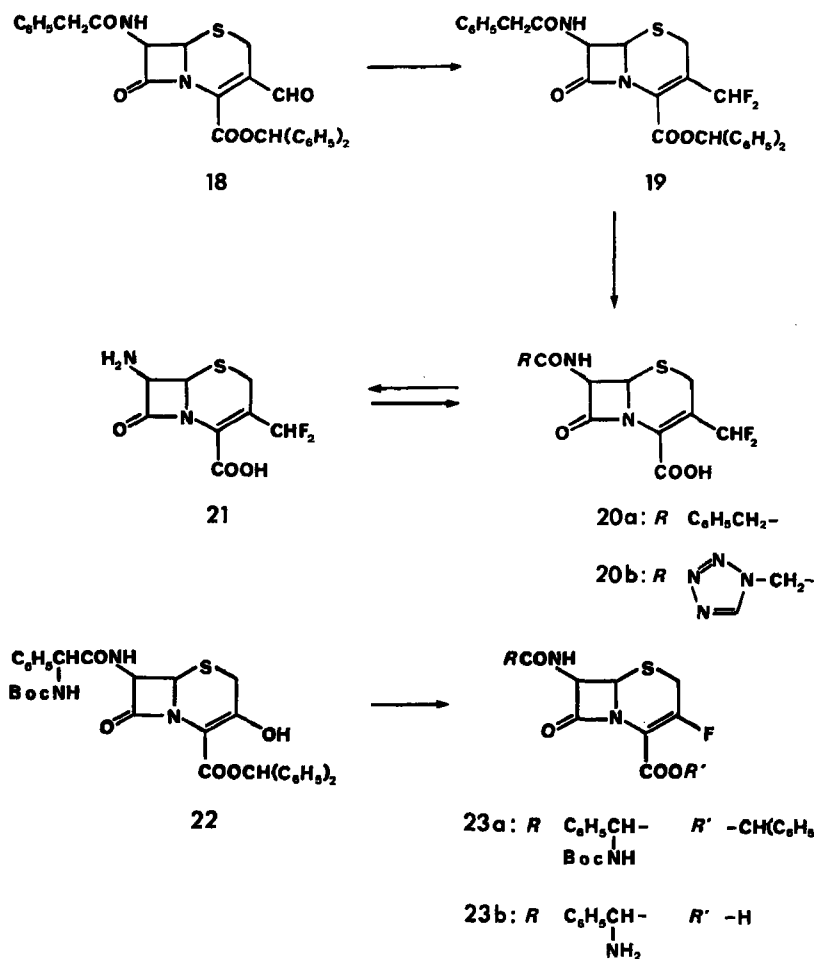
¹⁾ UV. in ethanol, wavelength of maxima in nm (ϵ); IR.: characteristic absorptions in μ ; NMR.: 100 MHz, chemical shifts relative to TMS ($\delta = 0$) in δ -values (ppm.), coupling constants in Hz, $ABF = AB$ -system with additional H-F coupling.

$J_{\text{H-F}} = 47/\text{CH}_2\text{F}$; 4.96 ($d \times d/J = 1$, $J_{\text{H-F}} = 4/\text{H-C}(4)$); 5.20 ($d/J = 4/\text{H-C}(6)$); 5.55 ($d \times d/J = 4$ and $9/\text{H-C}(7)$); 6.42 ($d \times d/J = 1$, $J_{\text{H-F}} = 4/\text{H-C}(2)$); 6.52 ($d/J = 9/\text{NHCO}$); 7.26 ($m/\text{C}_6\text{H}_5$); MS. (m/e): 364 (M^+), 305, 277, 190].

Attempts to prepare the Δ^3 -fluoromethyl compound **8** directly from **10** and CTT in CH_2Cl_2 , CHCl_3 or THF failed, and lactone **13** was the only product isolated. The same reaction in the presence of methanol or ethanol yielded ethers **11** (77%) or **12** (70%) respectively. These results represent a new method for the synthesis of 3-alkoxymethyl-cephalosporins [7]. For the preparation of the desired 3-fluoromethyl- Δ^3 -cephalosporins, fluorine therefore had to be introduced into a Δ^2 -derivative the double bond of which could subsequently be isomerized.

Alcohol **2b** was converted with CTT (1.0 eq.) in 1,2-dichloroethane (0° , 2 h) to fluoride **6b** (73%) [m.p. $182\text{--}184^\circ$; NMR. (CDCl_3): characteristic $-\text{CH}_2\text{F}$ pattern at 4.63 and 4.77 (ABF , $J_{\text{H-H}} = 11$; $J_{\text{H-F}} = 47$)]. Oxidation of **6b** with 3-chloroperbenzoic acid afforded **7** (73%), which was subsequently reduced to **8** with PCl_3 in DMF at -20° (68%) [8]. Cleavage of the diphenylmethylester with TFA/anisole [9] pro-

Scheme 2



vided the desired Δ^3 -carboxylic acid **9**, (70%) [m.p. 132–135°; UV. 259 (5600); IR. (nujol): 3.02, 5.60, 5.78, 6.06, 6.51; NMR. (DMSO- d_6): 5.15 ($d/J_{H-F} = 47/CH_2F$)].

Side chain cleavage [10] by treatment of **8** with PCl_5 at -5 to -10° gave nucleus **14** (74%), m.p. 130–135°. At -30° only 34% of **14** together with 44% of **15** were obtained after silicagel chromatography ($CH_2Cl_2/EtOAc$ 9:1). To our knowledge **15** is the first example of a phosphoramidate dimethylester resulting from deacylation of a cephalosporin derivative with PCl_5 /methanol. **14** was reacylated with the mixed anhydride from N-Boc-(D)- α -phenylglycine and isobutylchloroformate to give **16**, m.p. 116–118°, from which **17**, m.p. 168–172° (dec.) was obtained on treatment with TFA and anisole.

In contrast to the esters **8** and **16** the acids **9** and **17** were unstable in aqueous solution and on silicagel. Potentiometric determination indicated almost complete liberation of fluoride within 2 h at 20° in aqueous solution at pH 5.2 and a mixture of decomposition products was observed. **9** and **17** displayed only low antimicrobial activity *in vitro* and *in vivo*.

For the preparation of 3-difluoromethyl-3-cephems the readily available aldehyde **18** [11] (Scheme 2) was treated in dioxane with 7.0 eq. PST at room temperature for 1.5 h. Crystalline **19** could be isolated in 45% yield [m.p. 195–197°; UV.: 259 (7400); IR. (CH_2Cl_2): 5.55, 5.76, 5.90; NMR. ($CDCl_3$): 3.50 (s/H-C(2)); 3.60 (s/ CH_2CO); 4.91 ($d/J = 5/H-C(6)$); 5.88 ($d \times d/J = 5$ and $9/H-C(7)$); 6.17 ($d/J = 9/NH$); 6.67 ($t/J = 54/CHF_2$); 6.92 (s/ $COOCH$); 7.2–7.4 ($m/15$ arom. H)]. **19** was converted to the microbiologically active acid **20a** with TFA (0° , 15 min.) (80%) [m.p. 122–124°; UV.: 258 (6500); IR. (nujol): 5.58, 5.77, 6.02; NMR. (DMSO- d_6): 3.55 (s/ CH_2CO); 3.63 (s/H-C(2)); 5.18 ($d/J = 5/H-C(6)$); 5.81 ($d \times d/J = 5$ and $9/H-C(7)$); 6.87 ($t/J = 54/CHF_2$); 7.27 (s/5 arom. H); 9.14 ($d/J = 9/NH$); MS. (m/e): 368 (M^+)]. PCl_5 -cleavage of **20a** gave crude nucleus **21** [NMR. (DMSO- d_6 + DCl): 3.77 (s/H-C(2)); 5.2–5.4 ($m/H-C(6)$, H-C(7), NH_3^+); 6.90 ($t/J = 54/CHF_2$)], which was used for the preparation of analogous N-acylderivatives by known methods [12], e.g. **20b** [m.p. 130° dec.; UV.: 259 (6800); IR. (nujol): 5.57, 5.81, 5.96, 6.06, 6.40; NMR. (DMSO- d_6): 3.65 (s/H-C(2)); 5.19 ($d/J = 5/H-C(6)$); 5.37 (s/ CH_2CO); 5.83 ($d \times d/J = 5$ and $9/H-C(7)$); 6.85 ($t/J = 54/CHF_2$); 9.32 (s/tetrazole-H); 9.51 ($d/J = 9/NH$); MS. (m/e): 360 (M^+)].

The usefulness of PST as a fluorinating agent was further studied with **22** [13] as a substrate. 2 hours treatment of **22** with 3.0 eq. PST in CCl_4 at room temperature produced a reaction mixture, from which the 3-fluoro-3-cephem derivative **23a** could only be isolated in very low yield (3%) after exhaustive chromatographic purification [m.p. 148–151°; UV.: 258 (5500); IR. (CH_2Cl_2): 2.94, 5.58, 5.80, 5.90, 6.02, 6.70; NMR. (CD_3Cl): 1.36 (s/ $C(CH_3)_3$); 3.20/3.45 ($ABF/J = 18$, $J_{A-F} = 9/H-C(2)$); 4.84 ($d/J = 5/H-C(6)$); 5.18 ($d/J = 6/C_6H_5CH$); 5.63 ($d/J = 6/BocNH$); 5.91 ($d \times d/J = 5$ and $9/H-C(7)$); 6.88 ($d/J = 9/NH$); 6.92 (s/ $COOCH$); 7.1–7.3 ($m/15$ arom. H); $[\alpha]_D^{20} = +7^\circ$ (0.6%, dioxane). **23a** was converted with TFA to the amorphous, microbiologically active zwitterion **23b** [UV.: 253 (4700); IR. (nujol): 5.64, 5.85, 5.90, 5.98; NMR. (CD_3OD , DCl): 3.48/3.77 ($ABF/J = 18$, $J_{A-F} = 10/H-C(2)$); 5.07 (s/ C_6H_5CH); 5.09 ($d/J = 4.5/H-C(6)$); 5.77 ($d/J = 4.5/H-C(7)$); 7.47 (s/5 arom. H)].

Compounds **20a**, **20b** and **23b** were more stable than the 3-fluoromethyl derivatives already mentioned and proved to be appreciably more active against a broad spectrum of bacteria.

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266. ESR.-Studies of Nonalternant Radicals Structurally Related to Phenalenyl

by Fabian Gerson¹⁾, Joanna Jachimowicz¹⁾, Ichiro Murata²⁾,
Kazuhiro Nakasuji²⁾ and Kagetoshi Yamamoto²⁾

Physikalisch-Chemisches Institut der Universität Basel,
Klingelbergstrasse 80, 4056 Basel, Switzerland, and
Department of Chemistry, Faculty of Science,
Osaka University, Toyonaka, Osaka 560, Japan
(11. IX. 75)

Summary. The radical anion and the radical cation of azuleno[1,2,3-*cd*]phenalene (III) have been investigated by ESR. spectroscopy, along with the radical anion of 2-phenylazulene (IV). Also studied has been the neutral radical obtained by one-electron reduction of cyclohepta[*cd*]phenalenium-cation (VI[⊕]). Assignment of the proton coupling constants for the radical ions III^{•−}, III^{•⊕} and IV^{•−}, and the radical VI[•] is supported by comparison with the ESR. spectra of specifically deuteriated derivatives III-*d*₅^{•−}, III-*d*₅^{•⊕}, IV-*d*₂^{•−} and VI-*d*₁[•]/VI-*d*₁[•]. The experimental results are in full accord with qualitative topological arguments and predictions of HMO models. Whereas the radical anion III^{•−} exhibits π -spin distribution similar to that of IV^{•−}, the corresponding radical cation III^{•⊕} and the neutral radical VI[•] are related in this respect to phenalenyl (V[•]). It is noteworthy that oxidation of III by conc. H₂SO₄ yields a paramagnetic species (IIIa^{•⊕}) which has a similar – but not an identical – structure as the radical cation III^{•⊕} produced from III with AlCl₃ in CH₃NO₂.

We have reported previously [1] on the radical anion of azuleno[5,6,7-*cd*]phenalene (I) which resembles that of 6-phenylazulene (II) with respect to its ease of formation and π -spin distribution. A corresponding relationship is expected to hold for the radical anions of 2-phenylazulene (IV) and azuleno[1,2,3-*cd*]phenalene (III), a nonalternant hydrocarbon synthesized recently [2]. The radical anion of III should thus be adequately described by the formula III^{•−} which represents IV^{•−} linked to two isolated double bonds.

¹⁾ Universität Basel.

²⁾ Osaka University.