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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**

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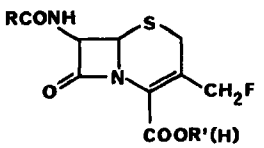
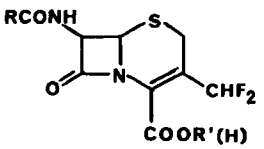
(9. IX. 75)

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.

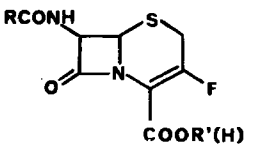
To our knowledge, 3-fluoromethyl-3-cephems (**1a**) and 3-difluoromethyl-3-cephem derivatives **1b** have not yet been described. 3-Fluoro-3-cephem derivatives of type **1c** have recently been disclosed in the patent literature [2].



1a



1b

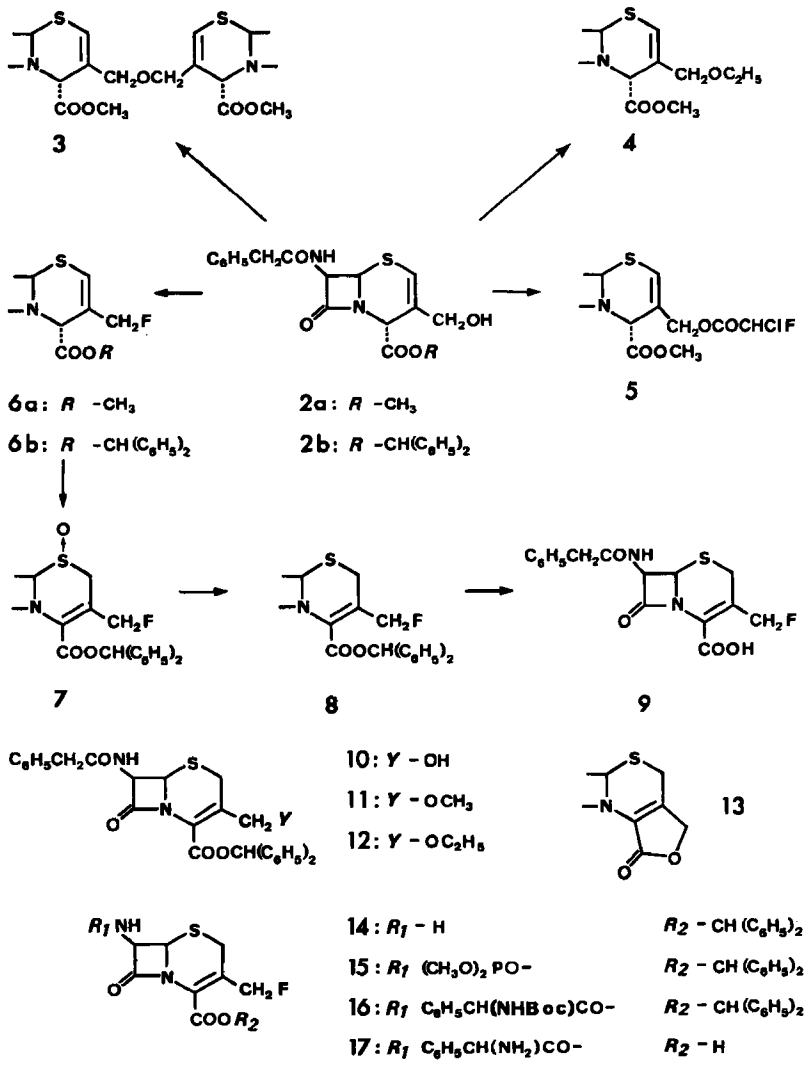


1c

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°; UV.[1]): 243 (13,500); IR. (nujol): 2.98, 5.62, 5.74, 6.04, 6.52; NMR. (DMSO-d_6): 3.58 (*s*/CH_2CO); 3.77 (*s*/OCH_3), 4.05/4.06 (*AB*/*J* = 16/CH_2O); 4.90 (*d*/*J* = 1/H–C(4)); 5.22 (*d*/*J* = 4/H–C(6)); 5.64 (*d* × *d*/*J* = 4 and 9/H–C(7)); 6.39 (*d*/*J* = 1/H–C(2)); 7.26 (*s*/C_6H_5); 7.50 (*d*/*J* = 9/NHCO)]; 2) *3-fluoromethyl-Δ²-cephem-ester* (**6a**) (36%) [m.p. 141–145°; 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



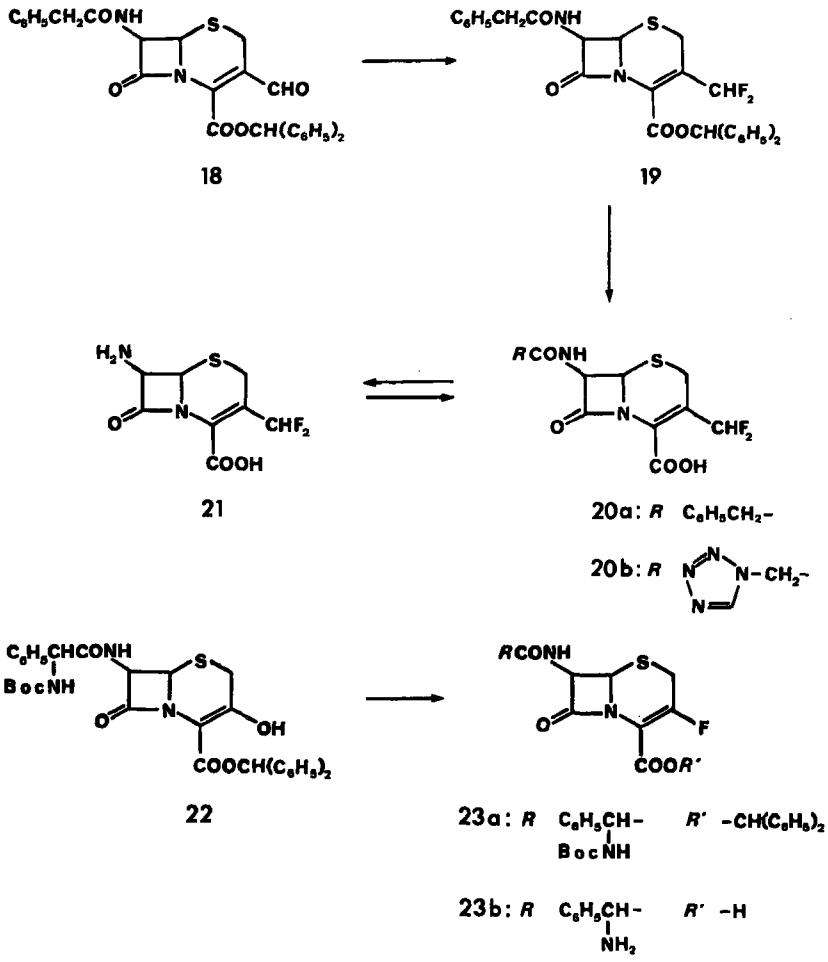
[1]) UV. in ethanol, wavelength of maxima in nm (ε); IR.: characteristic absorptions in μ; NMR.: 100 MHz, chemical shifts relative to TMS (δ = 0) in δ-values (ppm.), coupling constants in Hz, *ABF* = *AB*-system with additional H-F coupling.

$J_{H-F} = 47/CH_2F$); 4.96 ($d \times d/J = 1$, $J_{H-F} = 4$/H–C(4)); 5.20 ($d/J = 4$/H–C(6)); 5.55 ($d \times d/J = 4$ and 9/H–C(7)); 6.42 ($d \times d/J = 1$, $J_{H-F} = 4$/H–C(2)); 6.52 ($d/J =$ 9/NHCO); 7.26 (m/C_6H_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. 182–184°; NMR. ($CDCl_3$): characteristic $-CH_2F$ pattern at 4.63 and 4.77 (ABF, $J_{H-H} = 11$; $J_{H-F} = 47$)]. 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 phosphoramide 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*×*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*×*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*×*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*×*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); $[\alpha]_D^{20} = +7°$ (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 Gerson**[1]), **Joanna Jachimowicz**[1]), **Ichiro Murata**[2]), **Kazuhiro Nakasuji**[2]) and **Kagetoshi Yamamoto**[2])

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(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$^{\oplus}$). Assignment of the proton coupling constants for the radical ions III $\cdot^{\ominus}$, III $\cdot^{\oplus}$ and IV $\cdot^{\ominus}$, and the radical VI $\cdot$ is supported by comparison with the ESR. spectra of specifically deuteriated derivatives III-d_5 $\cdot^{\ominus}$, III-d_5 $\cdot^{\oplus}$, IV-d_2 $\cdot^{\ominus}$ and VI-d_1 $\cdot$ /VI-d_1' $\cdot$. The experimental results are in full accord with qualitative topological arguments and predictions of HMO models. Whereas the radical anion III $\cdot^{\ominus}$ exhibits π-spin distribution similar to that of IV $\cdot^{\ominus}$, the corresponding radical cation III $\cdot^{\oplus}$ and the neutral radical VI $\cdot$ are related in this respect to phenalenyl (V $\cdot$). It is noteworthy that oxidation of III by conc. H_2SO_4 yields a paramagnetic species (IIIa $\cdot^{\oplus}$) which has a similar – but not an identical – structure as the radical cation III $\cdot^{\oplus}$ produced from III with $AlCl_3$ in CH_3NO_2.

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 $\cdot^{\ominus}$ which represents IV $\cdot^{\ominus}$ linked to two isolated double bonds.

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