NEW ORALLY ACTIVE CEPHALOSPORINS *

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The synthesis of cephalosporins modified at C-3 and the effect of the substituents on the oral absorption is reviewed. Of the structural variants studied in the author's laboratory the 3-methoxy derivatives are of particular interest.

During the past decade considerable improvements have been made among the injectable cephalosporins by systematic variation of the acyl side chain attached to the amino group at C-7 and replacement of the acetoxy group at C-3' by different nucleophiles. Progress has been less evident among the oral cephalosporins, where only one further compound, cephradin, has become available since cephaloglycin and cephalexin were introduced into clinical practice in 1970. This paucity of tangible results does not, however, reflect the intensive research being conducted in many laboratories throughout the

* Dedicated to Prof. R.B. Woodward on the occasion of his 60th birthday.

world. It is the purpose of this review to summarize briefly some recent advances in this field with particular emphasis on work done in our own laboratories.

At the outset of our project, only cephaloglycin and cephalexin (Table 1) among a large number of cephalosporin derivatives were known to be absorbed from the gastrointestinal tract of laboratory animals and of man. This unique pharmacological property seemed to be related to the presence of the phenylglycyl side chain, a residue which in combination with the penicillin nucleus had previously provided the orally active broad spectrum antibiotic ampicillin.

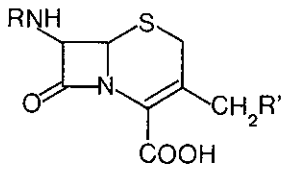
Cephalexin differs structurally from cephaloglycin in the substitution of a methyl group for an acetoxymethyl function at C-3. This slight structural change accounts for the differences in stability and pharmacological properties of the antibiotics. In aqueous solution cephalexin is much more stable than cephaloglycin, its half-life at pH 7.4 and 37° being approximately 20 hrs, whereas cephaloglycin has a half-life of about 1.5 hrs. Following oral administration to man cephalexin is absorbed almost quantitatively, produces therapeutically effective systemic concentrations and is excreted unchanged in the urine. Cephaloglycin is rather poorly absorbed, gives much lower peak serum concentrations and is metabolized to a large extent to the less active deacetyl derivative [1].

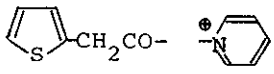
While antimicrobial activity can be assessed by well established methods, more elaborate experimentation, not easily adapted to the screening of a large number of compounds is

needed to detect oral absorption. At the beginning of our investigation it was eventually found that the ratio $\underline{R}^{(po/sc)}$ of the ED_{50}-values determined orally (po) and subcutaneously (sc) might be used to select derivatives which presumably would provide adequate blood levels in man after oral administration.

This is exemplified by the data in Table 1 [1]. Thus a clear

Table 1.



No.	R	R'	MIC [2] S.aur.	MIC [2] E.coli	ED_{50} [2] (S.aureus) po	sc	R^{po}/sc
Cex	$C_6H_5CH(NH_2)CO-$	-H	1.6	12.5	7.5	12	0.6
Ceg	$C_6H_5CH(NH_2)CO-$	$-OCOCH_3$	3.1	6.2	8	6	1.3
Cer			0.05	3.1	1.7	0.17	10
1	$C_6H_5CH_2CO-$	-H	1	>100	30	95	0.3
2	$C_6H_5CH_2CO-$	$-OCOCH_3$	0.2	25	30	3	10

Cex: Cephalexin; Ceg: Cephaloglycin; Cer: Cephaloridin

1) For the sake of simplicity we restrict the number of biological data to a minimum needed in our discussion. Staphylococcus aureus (S.aur.) and Escherichia coli (E.coli) are taken as representative species of gram-positive and gram-negative bacteria.

2) MIC : minimum inhibitory concentration in mcg/ml.

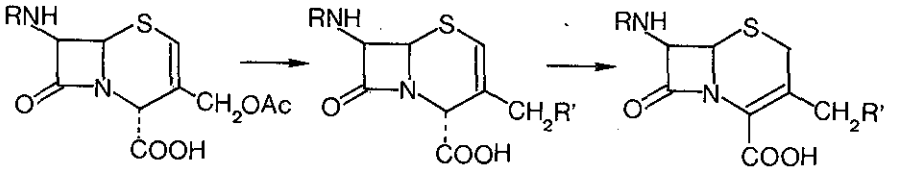
ED_{50} : dose in mg/kg affording protection against lethal infection in 50 % of treated mice.

difference between the two "oral" cephalosporins (cephalexin, cephaloglycin) and the "parenteral" cephaloridin can be seen if one compares the R-values. The po ED_{50}-value itself may not necessarily reflect a good oral absorption but rather a high antimicrobial activity as is the case for cephaloridin. The ED_{50}-values of the phenylacetyl analogue 1 of cephalexin do not represent an activity of practical interest. However, the R-value indicates a good oral absorption. This is in contrast to the results found with the corresponding analogue 2 of cephaloglycin. This and similar findings led us to believe that the pharmacological properties, in particular the oral absorption of a cephalosporin were strongly influenced by the substituent in the 3-position of the cephem nucleus. Since this substituent is electronically linked via the 3,4-double bond with the amide bond of the β-lactam ring, it was expected that its modification would influence both the antimicrobial activity and the chemical reactivity.

Therefore, in our search for orally active cephalosporins we directed our main efforts towards the modification of the substituents in the 3-position. R-values of ≤ 1 were taken as an indication of potential oral activity.

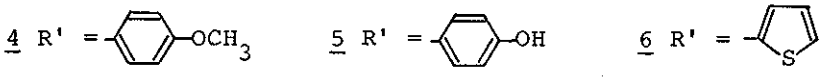
A first opportunity to enter a novel series of cephalosporins substituted in the 3-position with arylmethyl- and hetero-arylmethyl groups presented itself when it was found that the treatment of the iso-cephalosporanic benzhydryl ester 3a with trifluoroacetic acid in the presence of anisol gave a mixture of the ortho and para substituted anisyl deri-

vatives, the para isomer being the main product. Under similar conditions phenol and thiophene, as well as other types of aromatic C-nucleophiles underwent the same type of reaction [2].



3a

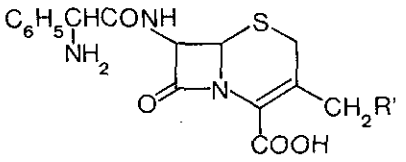
4a,b 5a,b 6a,b



a: R= $C_6H_5CH_2CO-$; b: R= $C_6H_5\underset{\underset{NH_2}{|}}{C}HCO-$

Isomerisation of the double bond by base catalysis or by the well established procedure involving the oxidation and reduction of sulfur [3] gave the Δ^3-isomers 4a-6a. PCl_5-cleavage [4] of the phenylacetamido side chain and reacylation furnished the phenylglycyl derivatives 4b-6b, which proved to be chemically rather stable and, therefore, were of some interest with regard to oral absorption. However, these cephalosporins were mainly active against gram-positive microorganisms (Table 2). Judging from the R-values it seemed questionable whether they would prove effective upon oral administration.

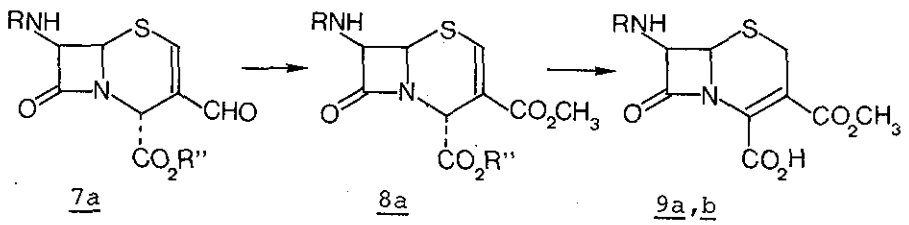
Table 2.



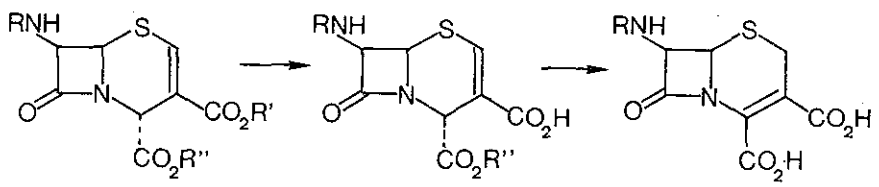
No.	R'	MIC S.aur.	MIC E.coli	ED_{50} po	ED_{50} sc	(S.aureus) R^{po}/sc
4b	p-C_6H_4-OCH_3	0.3	60	100	5	20
5b	p-C_6H_4-OH	0.3	10	30	5	6
6b		0.3	30	50	10	5

It is generally believed that the antimicrobial activity of β-lactam antibiotics is related to the reactivity of the β-lactam N-CO bond. In cephalosporins electron-withdrawing substituents at position 3 should enhance the electrophilic character of the β-lactam carbonyl and render it more susceptible to nucleophilic attack. As a consequence the activity might also be improved. On the basis of these rather speculative conceptions, methods were then sought for the preparation of compounds of this type.

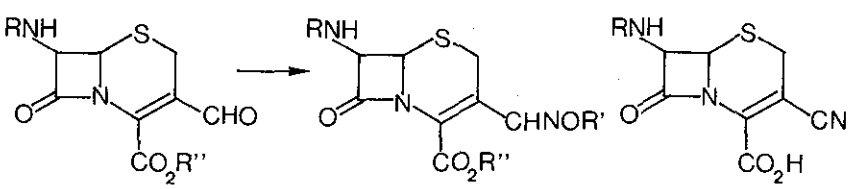
The 3-formylcephem esters obtained from the corresponding deacetyl derivatives by oxidation with DMSO/Ac_2O or with CrO_3/pyridine proved to be versatile intermediates for the synthesis of various cephems bearing electron-withdrawing substituents at C-3 [5].



7a 8a 9a,b



10a: R' $=CH_2CH_2Br$ 11a 12a



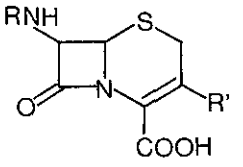
13a 14a: R' = CH_3 15a: R' = H 16a

a: R= $C_6H_5CH_2CO-$; b: R= $C_6H_5\underset{\underset{NH_2}{|}}{C}HCO-$; R" = $CH(C_6H_5)_2$

Oxidation of 7a with $NaCN/MnO_2$ in methanol according to Corey [6] gave the 3-methoxycarbonyl cephem 8a, which was converted into the Δ^3-acid 9a by established procedures. Derivatives with varied amide functions were prepared from 9a by removal of the phenylacetamido side chain and reacylation with appropriate residues. The dicarboxylic acid 12a was obtained in an analogous reaction sequence via the bromo-ethyl ester 10a as an intermediate. Additional compounds prepared from the 3-formyl cephem ester 13a included the methoxyimino and the oxyimino

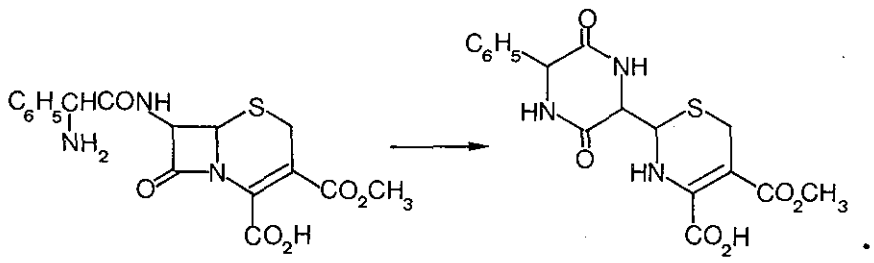
derivatives 14a and 15a. Hydrolysis of the benzhydryl ester group with trifluoroacetic acid gave the corresponding acid from 14a, whereas 15a suffered loss of water and formed the 3-cyano-cephem 16a.

Table 3.



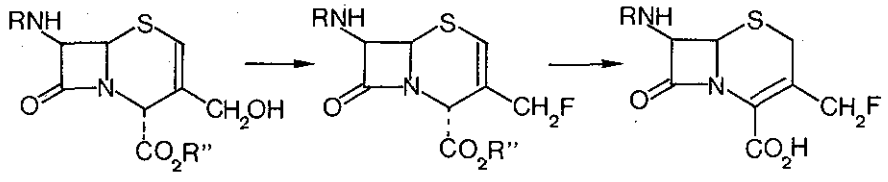
No.	R'	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	ED_{50} (S.aureus) sc	R^{po}/sc
9a	$-COOCH_3$	0.5	>100	100	80	1.2
9b		30	>100			
12a	-COOH	3.5	>100	>100	>100	
16a	-CN	0.4	>100	100	30	3.3

The rather disappointing activity (Table 3) of these new derivatives may be explained by their insufficient stability in the physiological pH-range. This was especially evident for the phenylglycyl derivative 9b, which formed the 1,4-diketopiperazine 17 under very mild conditions via intramolecular aminolysis of the β-lactam ring.



9b 17

In connection with our work on electron-withdrawing substituents we became also interested in fluorinated cephalosporins. These could be prepared using either 2-chloro-1,1,2-trifluorotriethylamine (CTT) or piperidine sulfur trifluoride (PST) as fluorinating agents [7]. Treatment of 18a with CTT in 1,2-dichlormethane gave inter alia the 3-fluoromethyl derivative 19a which was converted into the desired Δ^3-acid 20a via the usual oxidation/reduction procedure and ester hydrolysis. PCl_5-cleavage and reacylation then yielded the phenylglycyl derivative 20b. 20a and 20 b displayed only weak antimicrobial activity in vitro and in vivo (Table 4) probably because of their instability. Potentiometric titration indicated almost complete liberation of fluoride ions within 2 hrs (20°, pH 5.2).



18a 19a 20a,b

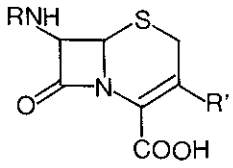
a: R= $C_6H_5CH_2CO$- ; b: R= $C_6H_5CH(NH_2)CO$- ; R" = $CH(C_6H_5)_2$

The 3-difluoromethyl-3-cephem 21a was obtained in moderate yield from the readily available 3-formyl compound 13a by reaction with PST and hydrolysis with trifluoroacetic acid. Its activity turned out to be similar to that of 20a (Table 4). The phenylglycyl derivative 21b, however was inactive and had a half-life of only 0.5 hrs. (phosphate buffer pH 7.4, 37°).

13a 21a,b

a: R= $C_6H_5CH_2CO-$; b: R= $C_6H_5\underset{\underset{NH_2}{|}}{C}HCO-$; R" = $CH(C_6H_5)_2$

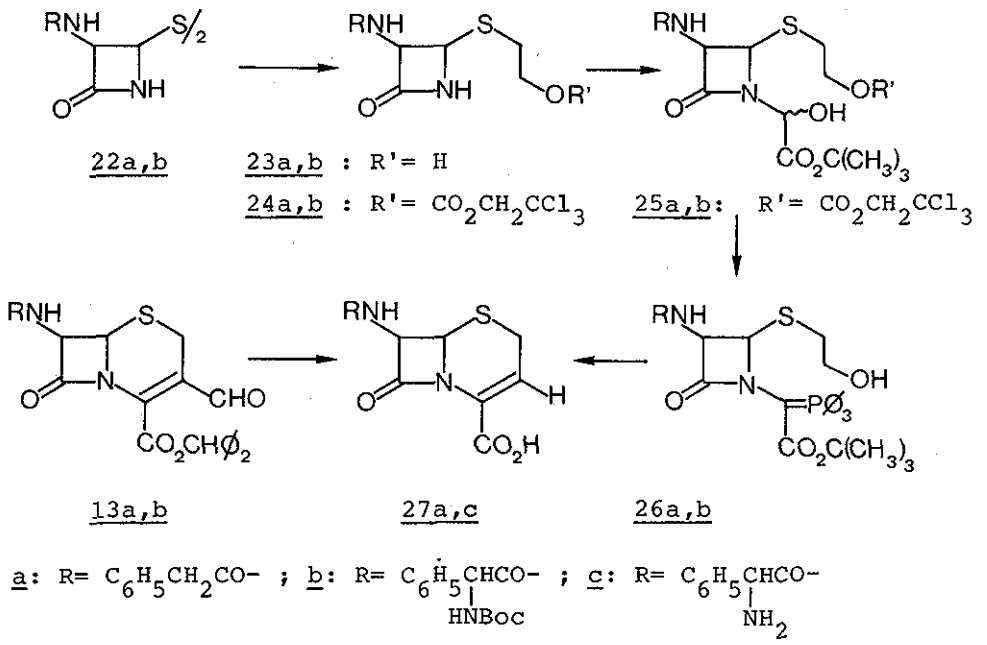
Table 4.



No.	R'	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	ED_{50} (S.aureus) sc	R^{po}/sc
20a	$-CH_2F$	5	>100	>100	60	>1.7
20b	$-CH_2F$	2	20	20	20	1
21a	$-CHF_2$	3	80	80	55	1.4
21b	$-CHF_2$	>100	>100	>100	>100	

In view of these results which further convinced us of the highly influential rôle of the substituent at C-3, the 3-unsubstituted cephem became an attractive target.

This type of compound could be synthesized for the first time by way of an elaborate sequence starting from the disulfides 22a,b, compounds available either by total synthesis or by degradation of penicillins [8]. Upon reduction of the disulfides with zinc in the presence of ethylene oxide, the intermediate mercaptides were trapped and the carbinols 23a,b, formed in acceptable yield. The two missing carbons were then introduced by the addition of glyoxylic ester (23a,b → 25a,b), following a procedure developed by Woodward and coworkers [9]. Conversion into the phosphoranes 26a,b and oxidation with DMSO/acetic anhydride led to the desired compounds 27a,c, after removal of the protecting groups. Owing to the fairly large number of steps this synthesis was not suited to the preparation of larger quantities of material. A more practical alternative became available when it was found that the 3-formyl cephems 13a,b could be smoothly decarbonylated by treatment with tris-(triphenylphosphine)rhodium chloride in toluene [10].

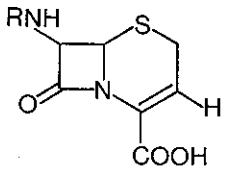


a: R= $C_6H_5CH_2CO-$; b: R= $C_6H_5\underset{\underset{HNBoc}{|}}{C}HCO-$; c: R= $C_6H_5\underset{\underset{NH_2}{|}}{C}HCO-$

Preliminary tests (Table 5) indicated that 27c had interesting antimicrobial properties against a broad spectrum of bacteria. Furthermore, from the R-values of the compounds it was assumed that the new cephem-nucleus would be efficiently absorbed from the gastrointestinal tract. The in vitro antibacterial activity of 27c against gram-positive and gram-negative bacteria was found to be approximately equal to that of cephalexin, when determined at pH 6.5 [11]. At pH 7.4 27c was several times less active indicating that its stability in the neutral pH range was rather limited. The half-life in serum and phosphate buffer of pH 7.4 was 1.5 hrs at 37°. In vivo this instability did not manifest itself and the therapeutic

effects in mice compared favourably with those of cephalexin. After oral administration the compound was well absorbed in laboratory animals and also in human volunteers.

Table 5.

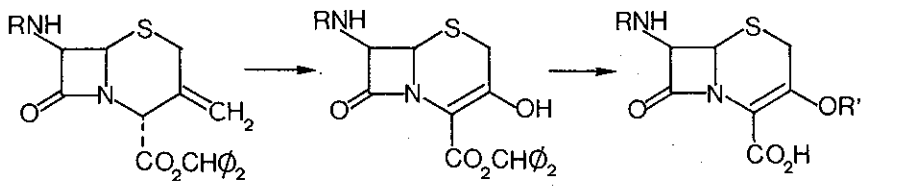


No.	R	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	sc	R^{po}/sc
27a	$C_6H_5CH_2CO-$	3	>100	8	6	1.3
27c	$C_6H_5\underset{\underset{NH_2}{|}}{C}HCO-$	2.5**)	3.5**)	2.7	16	0.2
	Cephalexin	1.6	12.5	7.5	12	0.6
**)	MIC determined at pH 6.5					

A first objective, the synthesis of a new orally active broad spectrum cephalosporin, had thus been accomplished. The interesting properties of this compound prompted us to concentrate our efforts on the synthesis of cephalosporins bearing heteroatom substituents directly attached to the 3-position.

A key intermediate for the preparation of such derivatives, the 3-hydroxycephem ester 29a, was obtained by ozonolysis of a 3-methylene cepham 28a. Alkylation of the enol function and removal of the protecting groups then provided access to a

series of 3-alkoxy derivatives, [3] 30b-33b. In addition the 3-unsubstituted cephem 27c could also be prepared from 29a by reduction with sodium borohydride and elimination of water [12].

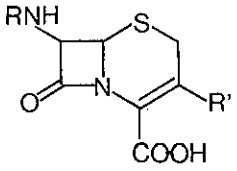


28a 29a

a: R= $C_6H_5CH(NHBoc)CO-$ b: R= $C_6H_5CH(NH_2)CO-$

30b R' = CH_3
31b R' = CH_2CH_3
32b R' = $(CH_2)_3CH_3$
33b R' = $CH_2C_6H_5$

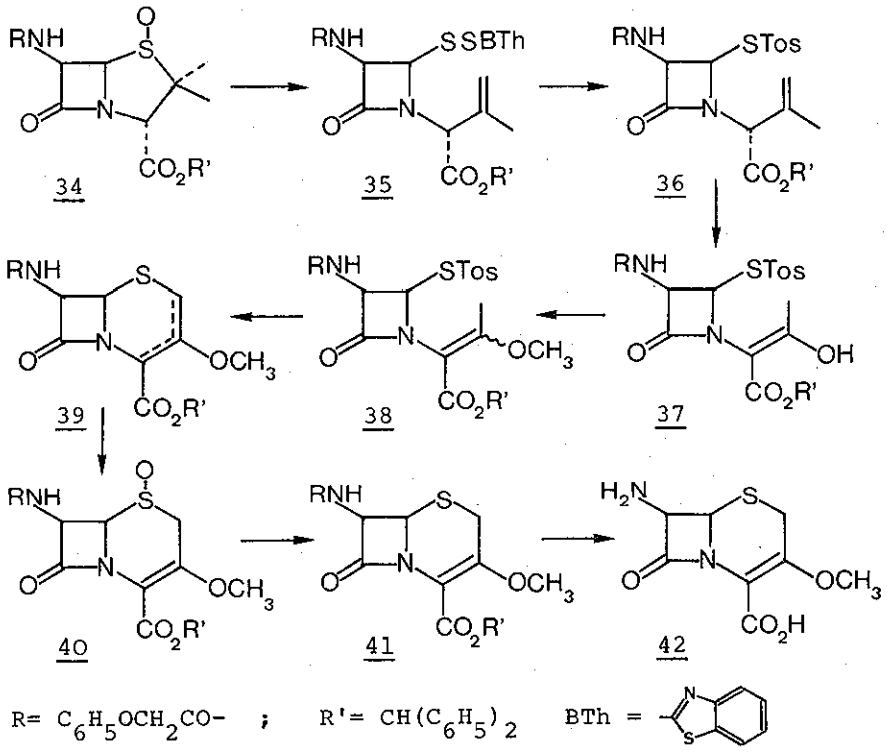
Table 6.



No.	R'	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	sc	R^{po}/sc
30b	$-OCH_3$	3.1	3.1	7.5	10	0.7
31b	$-OCH_2CH_3$	0.4	5	10	14	0.7
32b	$-OCH_2CH_2CH_2CH_3$	0.4	30	20	20	1
33b	$-OCH_2C_6H_5$	0.05	30	15	30	0.5

3) The 3-methoxy derivative 30b has been independently prepared by Chauvette and Pennington. These workers have also synthesized the 3-chloro and 3-bromo-cephems by reacting hydroxy esters with halogenating reagents [13].

The preliminary biological evaluation (Table 6) of these new antibiotics showed that in the phenylglycyl series the 3-methoxy-cephem compared favourably with cephalexin. Our interest in these derivatives prompted us to seek chemical routes using the more readily available natural penicillins as starting materials. Efforts conducted in close collaboration with the Woodward Research Institute in Basle culminated in a practical synthesis of the 3-methoxy nucleus 42 [14] [4].



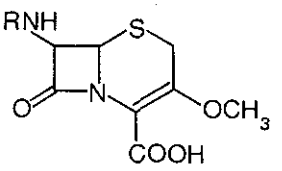
4) R.B. Woodward, 4th Int. Symp. on Synthesis in Org. Chem. Cambridge, UK, July 1975.

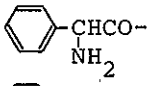
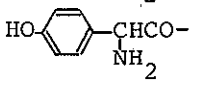
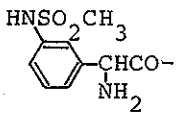
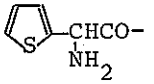
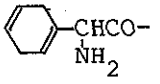
The sulfoxide ester of penicillin V, 34 when treated with mercaptobenzthiazole according to Kamiya et al., [15] gave the disulfide 35, which reacted smoothly with the silver salt of p-toluenesulfinic acid to the thiosulfonate 36. Alternatively 36 could also be obtained directly from 34 by reaction with p-toluenesulfonyl cyanide. Removal of one carbon atom by ozonolysis and methylation of the enol ester afforded a mixture of enol ethers 38, which cyclized upon treatment with DBU to a $\Delta^2/\Delta 3$-mixture of 3-methoxy cephems, 39. After the usual oxidation/reduction procedure the mixture of isomers was then converted into the desired $\Delta 3$-compound 41. Hydrolysis of the benzhydrylester group and removal of the side chain by PCl_5-cleavage gave the 7-amino-3-methoxyceph-3-em-4-carboxylic acid 42, in a good overall yield. With the 3-methoxy nucleus readily available, a number of derivatives were then prepared by acylation of the amino group at C-7.

Biological evaluation showed that the glycyl type compounds 43-46 generally displayed potent inhibitory activity against gram-positive and gram-negative bacteria in vitro and in vivo as well as promising R-values (Table 7).

On the basis of its pronounced bactericidal effect and its excellent chemotherapeutic and pharmacological properties the 1,4-cyclohexadienylglycyl derivative 46 [16] was eventually selected for further study. In human volunteers 46 was effectively absorbed after oral administration and was excreted unchanged in the urine to the extent of 80-90 %.

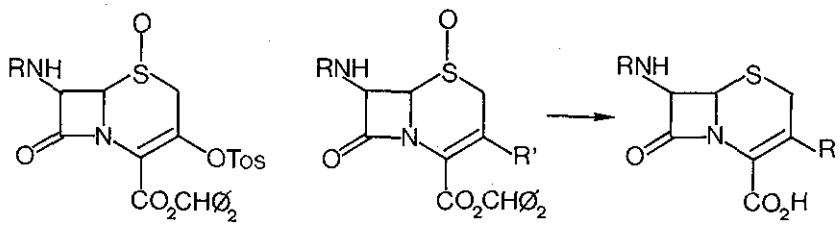
Table 7.



No.	R	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	sc	R^{po}/sc
30b		3	3	7.5	10	0.7
43		1	3	5	10	0.5
44		3	3	1.4	2.8	0.5
45		1.6	6	17	15	1.1
46		0.6	2.5	3	4	0.8

These encouraging results prompted us to search for means of preparing additional 3-heterosubstituted cephems. The functionalisation of the cephem 3-position with sulfur was accomplished by reacting the tosylate sulfoxide 47a (derived from 29a) with mercaptans [17]. Thus treatment with methylmercaptan, thiophenol or thioglycolic methyl ester and diisopropylethylamine gave the corresponding 3-thioethers 48a-50a in variable yields. Oxidation of 48a with m-chloroperbenzoic acid gave the 3-methylsulfonylderivative 51a as an additional structural variant. The N-methyltetrazolylthio moiety could best be

introduced by taking recourse to the more reactive mesylates (⟶ 52a). The free acids 53b-57b needed for biological evaluation were prepared after reduction of the sulfoxide function with PCl_3 by removal of the protecting groups with trifluoroacetic acid.



47a

a: R = C_6H_5CHCO- (NHBoc)

b: R = C_6H_5CHCO- (NH_2)

48a R' = SCH_3 → 53b

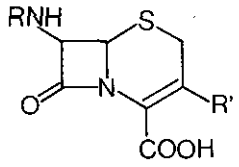
49a R' = SC_6H_5 → 54b

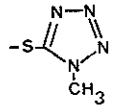
50a R' = $SCH_2CO_2CH_3$ → 55b

51a R' = SO_2CH_3 → 56b

52a → 57b

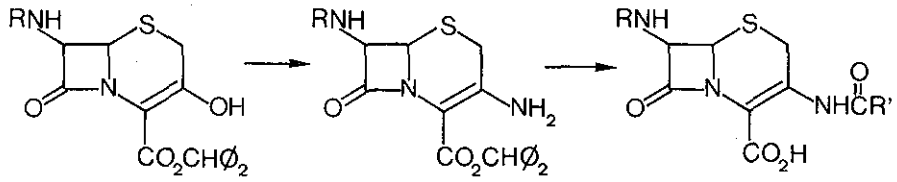
Table 8.



No.	R'	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	sc	R^{po}/sc
53b	$-SCH_3$	0.3	3	4	3	1.3
54b	$-SC_6H_5$	10	>100	>100	10	>10
55b	$-SCH_2CO_2CH_3$	60	>100	7	12	0.6
56b	$-SO_2CH_3$	>100	>100	>100	>100	
57b		60	>100	>100	80	>1

Among these thioethers the methylthio compound 53b displayed potent inhibitory activity in vitro and in vivo comparable to that of the corresponding oxygen analogue (Table 8). However, its stability was distinctly inferior and its half-life as determined in phosphate buffer at pH 7.4 and 37° was only 2.5 hrs. As was the case for the 3-methoxycarbonylcephem 9b, intramolecular aminolysis of the β-lactam took place in aqueous solution with formation of a diketopiperazine derivative. The discrepancies seen between the in vitro and the in vivo results (54b, 55b) can also be attributed to the instability of the compounds.

Cephems functionalized with nitrogen substituents at the 3-position proved readily accessible when it was found that the 3-hydroxycephem ester 29a could be converted into the 3-aminocephem 58a by reaction with NH_4Cl and pyridine in ethanol [17]. As might be expected from a vinylogous carbamic ester derivative 58a proved rather resistant towards acylations, which necessitated quite vigorous conditions. In the event 59b and 60b were prepared by reaction with the appropriate acid chlorides and 61b with furoyl isocyanate.

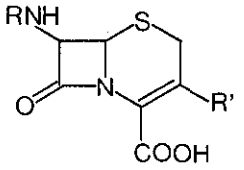


29a 58a 59b R'= CH_3; 60b R'= $CH_2C_6H_5$; 61b R'= NHCO-furyl

a: R= $C_6H_5CH(NHBoc)CO-$; b: R= $C_6H_5CH(NH_2)CO-$

These compounds substituted in 3-position with nitrogen, showed only a weak antimicrobial activity (Table 9).

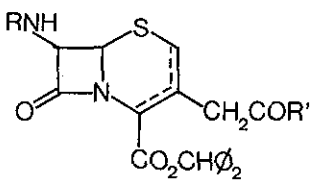
Table 9.



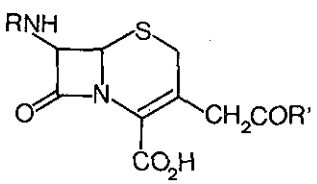
No.	R'	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	sc	R^{po}/sc
59b	$-NHCOCH_3$	4	>100	>100	35	>3
60b	$-NHCOCH_2C_6H_5$	1	>100	>100	55	>2
61b	-NHCONHCO- 	0.8	25	150	90	1.7

Having succeeded in synthesizing a series of hetero-substituted cephems, we then examined the Wittig-reaction of 29a with stabilized phosphor-ylids as a means of introducing a carbonylmethyl function in position-3 [18]. Owing to their rather poor accessibility, compounds of this type had not been studied extensively. This approach proved effective, and 62a, 63a and 64a were obtained as mixtures of $\Delta 2$/$\Delta 3$-isomers by heating 29a with the appropriate phosphoranes. The transformation into the corresponding $\Delta 3$-acids 65b, 66b was then car-

ried out by the usual three step procedure. Through a sequence of straightforward steps 64a was converted into the diacid 67b and the amides 68b and 69b.



62a R' = OCH_3
63a R' = CH_3
64a R' = $CH_2C_6H_4NO_2$

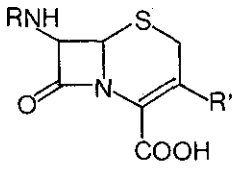


65b R' = OCH_3
66b R' = CH_3
67b R' = OH
68b R' = NH_2
69b R' = NHC_6H_5

a: R = $C_6H_5CH(HNBoc)CO-$; b: R = $C_6H_5CH(NH_2)CO-$

Among these derivatives 65b and 66b showed antibacterial properties of some interest (Table 10). Compared with cephaloglycin, with which it is isomeric, 65b proved twice as stable in phosphate buffer of pH 7.4. As was anticipated from the low R-value the compound was well absorbed after oral administration to dogs and gave peak serum concentrations similar to those of cephalexin.

Table 10.



No.	R'	MIC S.aur.	MIC E.coli	ED_{50} (S.aureus) po	sc	R^{po}/sc
65b	$-CH_2COOCH_3$	3	10	3	6	0.5
66b	$-CH_2COCH_3$	0.5	20	4	4	1
67b	$-CH_2COOH$	20	40	>100	>100	
68b	$-CH_2CONH_2$	1.6	50	45	15	3
69b	$-CH_2CONHC_6H_5$	1.6	>100	>100	45	>2

To conclude the discussions, we may summarize our results as follows: in cephalosporins the combination of glycyl-type side chains with various substituents at C-3 results in large differences in activity and stability. Interesting orally active broad spectrum antibiotics can result out of this group of cephalosporins if an optimal balance between the factors governing activity and stability is achieved. Of the numerous structural variants studied recently in our laboratories, cephems bearing a methoxy group at C-3 deserve particular mention in view of their usefulness as orally active broad spectrum antibiotics.

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