1,3-Dipolar Cycloaddition Reactions of Vinylcephalosporins with Diazoalkanes

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The vinylcephalosporin (**1**) undergoes a regio- and stereoselective 1,3-dipolar cycloaddition with diazomethane to give novel cephalosporins, a 3-pyrazolinocephem (**4**) and a double adduct (**5**). The vinylcephalosporin sulphoxide (**2**) gives only the pyrazolinocephem (**7**). In the reaction with diphenyldiazomethane upon heating the initially formed pyrazolines decompose and cyclopropylcephalosporin (**9**) formation takes place. The determination of the structures and stereochemistry of these compounds is also described.

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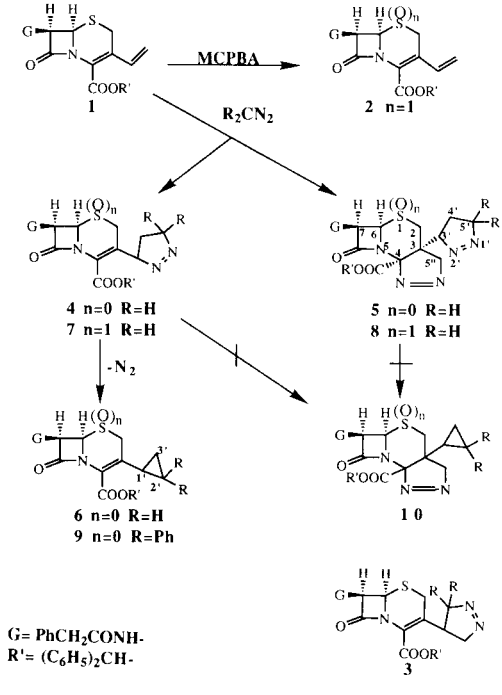
In our laboratory we study the cycloaddition reactions of cephalosporin compounds. We found that the Δ^3 double bond of cephems is relatively unreactive towards diazoalkanes [2]. The reaction was complete only after several days even with the most reactive diazomethane when 3,4-pyrazolinocepham formation took place. Bulky diazoalkanes, such as diphenyldiazomethane and ethyl diazoacetate do not undergo this cycloaddition.

In the reactions of 2-methylenecephalosporins with a range of diazoalkanes [3] the initially formed pyrazolines decomposed to 2-spirocyclopropylcephalosporins and the reactions were complete after 5 to 30 minutes at -5° and in a highly stereoselective manner. The endo double bond of the dihydrothiazine moiety remained intact.

In this paper we report a novel utilisation of the

Scheme 1



1,3-dipolar cycloadditions in cephalosporin chemistry where new types of cephalosporins form in the reaction of 3-vinylcephalosporins and diazoalkanes. Our aim was to establish the possible regio- and stereoselective nature of these cycloadditions.

When we consider the similarities between the conjugated system of our starting materials, the vinylcephems (**1** and **2**) (Scheme 1) and that of the 2-methylenecephalosporins (Figure 1) we can expect that the sterically less hindered vinyl double bond of vinylcephems undergoes 1,3-dipolar cycloadditions with different diazoalkanes more easily and less selectively than the exo double bond of the 2-methylenecephems. Surprisingly, this is not in the case.

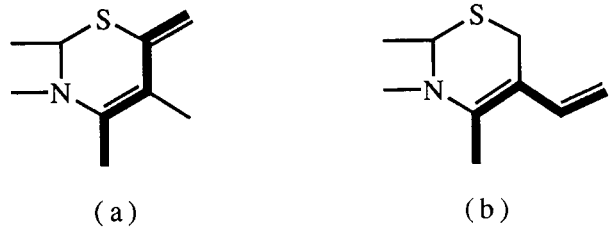


Figure 1. The conjugated system of vinylcephalosporins (**b**) and 2-methylenecephalosporins (**a**).

When compound **1** (Scheme 1), prepared by literature methods [4], was allowed to react with a large excess of diazomethane at room temperature there was a single product after 5 minutes (tlc) but before completion of the reaction (1 hour) the formation of two additional products was observed in differing amounts.

In the ^{1}H nmr spectrum of the initially formed (major) product the signals of vinyl hydrogens were not observable and five multiplets appeared (Table 2) (compound **4**). Couplings were observed among all of the new protons (COSY) showing that they are not separated by the -N=N- bond, *i.e.* the molecule is not an "α-adduct" of type **3**. However, these data did not preclude the possibility of a cyclopropane structure (**6**). The ^{13}C nmr spectrum of the molecule (Table 3) contains two new signals in the region of $=N-CH_2$ (δ 37-58) and one other in the region of $-C-CH_2$ (δ 21-45) in spite of the signals of vinyl carbons. Based on

Table 1
Physical and Analytical Data for Cephalosporins **1, 2, 4, 5, 7** and **9**

Compound	mp,°	Yield, %	Molecular Formula	Analyses, % Calcd./(Found) C	H	N	IR, cm^{-1} (β-lactam)
1	196-197	52	$C_{30}H_{26}N_2O_4S$	70.59 (70.63)	5.09 (5.13)	5.49 (5.27)	1780
2	213-215	97	$C_{30}H_{26}N_2O_5S$	68.44 (68.56)	4.94 (4.96)	5.32 (5.29)	1780
4	104-107	34.3	$C_{31}H_{28}N_4O_4S$	68.11 (67.98)	5.07 (5.11)	10.14 (10.21)	1785
5	111-115	19.8	$C_{32}H_{30}N_6O_4S$	64.65 (64.52)	5.05 (5.19)	14.14 (14.03)	1785
7	221-223	A:87.5 B:62.5	$C_{31}H_{28}N_4O_5S$	65.49 (65.53)	4.93 (5.12)	9.86 (9.70)	1790
9a,b	87-90	30.2	$C_{43}H_{36}N_2O_4S$	76.33 (76.21)	5.32 (5.41)	4.14 (4.08)	1780 (broad)

Table 2
^1H NMR and MS Data for Compounds **1, 2, 4, 5,** and **9**

Compound	^1H nmr [a], ppm	MS
1	3.3 and 3.6 (ABq, 2H, SCH_2), 3.56 (s, 2H, G-CH_2), 4.9 (d, 1H, H6), 5.24 (d, 1H, vinyl-CH_2-H_A), 5.39 (d, 1H, vinyl-CH_2-H_B), 5.83 (dd, 1H, H7), 6.64 (d, 1H, NH), 6.9 (s, 1H, BH), 7.0 (dd, 1H, vinyl-CH), 7.1-7.5 (m, 15H, arom)	ei: 510, (M^+)
2	3.5 and 4.4 (ABq, 2H, SCH_2), 3.55 and 3.7 (ABq, 2H,G-CH_2), 4.95 (d, 1H, H6), 5.35 (d, 1H, vinyl-CH_2-H_A), 5.6 (d, 1H, vinyl-CH_2-H_B), 5.9 (dd, 1H, H7), 6.9 (dd, 1H,v inyl-CH), 6.95 (s, 1H, BH), 7.1-7.55 (m, 15H, arom), 8.52 (d, 1H, NH)	ei: 526 (M^+)
4	1.1 and 2.1 (m, 2H, 4'-CH_2), 2.8 and 3.7 (ABq, 2H, SCH_2), 3.75 and 3.85 (ABq, 2H, G-CH_2), 4.05 and 4.9 (m, 2H, 5'CH_2), 5.05 (d, 1H, H6), 5.2 (m, 1H, 3'-CH), 5.9 (dd, 1H, H7), 6.05 (d, 1H, NH), 6.95 (s, 1H, BH), 7.1-7.3 (m, 15H, arom)	ci: 553 (M^++1)
5	0.9-1.1 (m, 2H, 4'-CH_2), 1.75 and 1.95 (ABq, 2H, SCH_2), 3.8 (s, 2H, G-CH_2), 3.95 and 4.5 (m, 3H, 5'-CH_2+3'-CH) 4.85 (d, 1H, H6), 5.45 and 5.65 (ABq, 2H, 5''-CH_2), 5.6 (dd, 1H, H7), 6.05 (d, 1H, NH), 6.95 (s, 1H, BH), 7.1-7.3 (m, 15H, arom)	ei: 566 (M^+-28) Fab: 594 (M^+)
7	1.1 and 2.1 (m, 2H, 4'-CH_2), 2.97 and 3.25 (ABq, 2H, SCH_2), 3.55 (s, 2H, G-CH_2), 4.02 and 4.78 (m, 2H, 5'-CH_2), 4.52 (d, 1H, H6), 5.43 (m, 1H, 3'-CH), 6.09 (dd, 1H, H7), 6.95 (s, 1H, BH), 7.05-7.5 (m, 15H, arom)	ei: 568 (M^+)
9a,b	**9a:** 1.39, 1.74 and 3.77 (3t, 3H, cyclopropyl-Hs), 1.96 and 2.84 (ABq, 2H, SCH_2), 3.57 (s, 2H, G-CH_2), 4.4 (d, 1H, H6), 5.6 (dd, 1H, H7), 6.5 (d, 1H, NH), 6.9-7.8 (m, 31H, NH+arom) **9b:** 1.42, 1.65 and 2.9 (3t, 3H, cyclopropyl-Hs), 2.14 and 2.63 (ABq, 2H, SCH_2), 3.55 (s, 2H, G-CH_2), 4.7 (d, 1H, H6), 5.6 (dd, 1H, H7), 6.1 (d, 1H, NH), 6.9-7.8 (m, 31H, NH+arom)	ei: 676 (M^+)

[a] In the case of **1, 4, 5, 7** and **9** the solvent was deuteriochloroform and in the case of **2** dimethyl-d_6 sulphoxide.

these findings the structure of the initially formed main product is **4**. The ms and elemental analyses (Table 1 and 2) corroborated this establishment. Only one of the two possible C-3' stereoisomers was formed in a quantitatively **stereoselective** reaction. The molecule is a "β-adduct" (**4**) (the new carbon-carbon bond formed at the β-position to carbon C-3), *i.e.* the reaction is **regioselective**. This was expected by the FMO-theory [5], too.

The ^1H and ^{13}C nmr spectra of the other major product is very similar to those of **4** but both contain a new -CH_2- signal characteristic of 3,4-pyrazolinocephams indicating the pyrazolino-pyrazolylcepham (**5**) structure of the molecule. In the light of our earlier findings [2] this fast reaction of the Δ^3 bond was unexpected. Isomerisation of the -N=N- double bond did not take place [2,6].

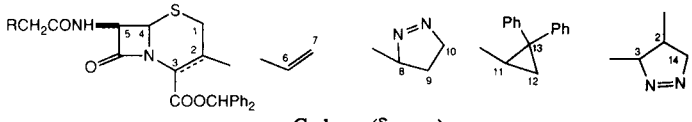
Unfortunately, the minor product of the reaction was not formed in sufficiently large amount to rigorously establish the structure but the ^1H nmr spectrum of the molecule is very similar to that of **5**, indicating that these compounds are probably different only in the configurations at C-3 and C-4.

In order to gain further insight into the nature of the cycloaddition, the vinylcephalosporin sulphoxide (**2**) was also prepared. This compound underwent cycloaddition reaction with diazomethane only after 4 hours and a single product (**7**) was observed in a **stereo-** and **regioselective** reaction. This molecule was identical with the peracid oxidation product of **4**. Double adduct (**8**) did not form.

The stereochemistry at C-3' depends upon the direction of attack of diazomethane. The β-face of the cephalosporin molecule can be regarded as the *re*-side of the dienophile. As it is seen from Figure 2 [7], there is a 4% nOe between 2β-H and one of the pyrazoline 4'-H protons. This information alone is not enough to elucide the

Table 3

^{13}C NMR Data for the Cephalosporins **1, 2, 4, 5, 7** and **9**



Carbons (δ, ppm)

Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	24.11	133.86	124.23	57.66	59.29	129.42	117.98							
2	37.14	134.58	124.31	65.09	58.43	130.38	119.76							
4	23.53	135.67	124.05	57.93	58.98	-	-	87.68	22.52	76.67				
5	27.62	104.87	46.82	55.06	60.49	-	-	90.63	19.76	76.85	-	-	-	87.89
7	44.02	133.97	123.84	67.09	58.99	-	-	88.07	23.58	76.74				
9a	26.31	133.06	125.81	57.50	58.92	-	-	-	-	-	27.57	18.82	37.75	
9b	26.31	133.06	125.81	58.21	58.92	-	-	-	-	-	28.70	18.82	37.75	

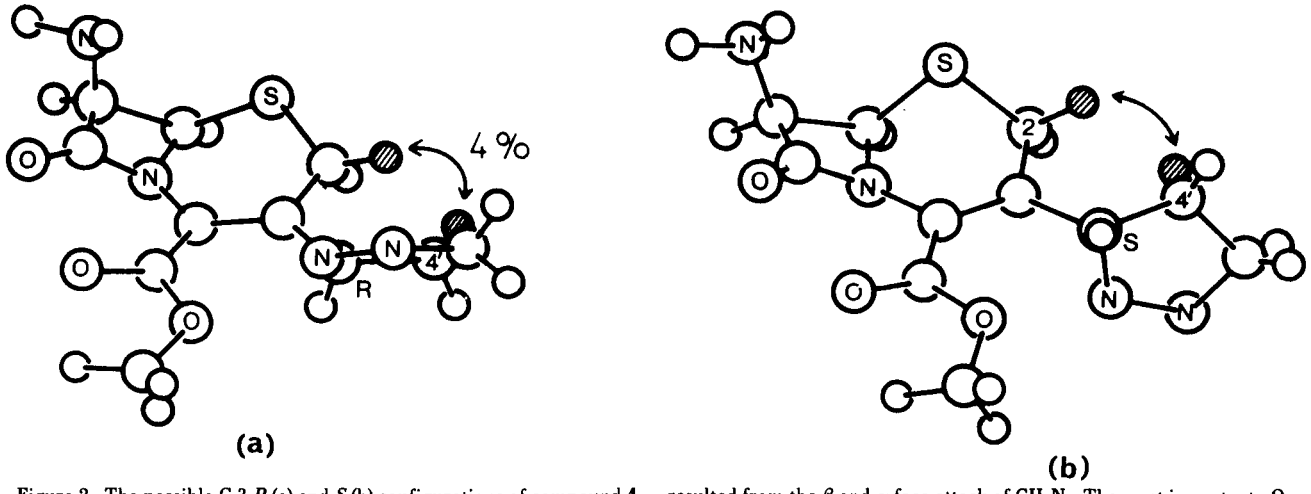


Figure 2. The possible C-3 *R* (a) and *S* (b) configurations of compound **4**, resulted from the β and α face attack of CH_2N_2. The most important nOe value is also shown. For clarity, the 7-acylamido side-chain and the benzhydryl moiety of 4-ester group are omitted.

Figure 2

stereochemistry at C-3'. A simple molecular modelling experiment shows that on rotating the pyrazoline ring around the C-3 - C-3' axis, the two hydrogens are in close contract of about 1.75 Å after the minimalization of conformational energy. This is smaller than the sum of the VDW radii. Moreover, the bulky C-4 ester group totally restricts the rotation of the pyrazoline group. Figure 3 shows the relative energy changes *vs* Θ dihedral angle (C-4 - C-3 - C-3' - C-4') for C-3 *R* and *S* isomers. The above mentioned nOe could be observed in two conformations of each of the stereoisomers, respectively. The markings on the energy curves of Figure 3 correspond to Θ values of these conformers and reveal that the adoptation of a suitable conformation in the case of *R* isomer (■) is far less favourable than that in the *S* isomer (**x**). Thus we can deduce that the molecules **4** and **7** have probably the C-3'*S* configuration (Structure **b**, Figure 2) and they are formed by the attack of the diazomethane from the less hindered α-face of the cephalosporin in completely **stereoselective** reactions.

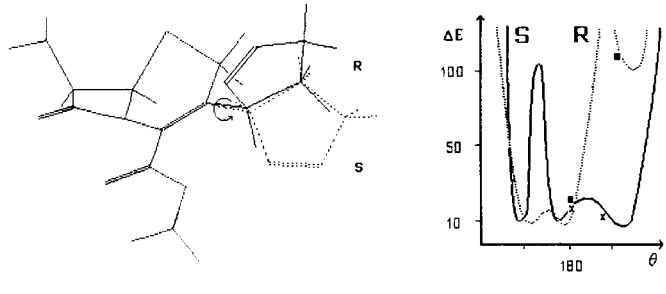


Figure 3. Changes in conformational energy when the 3-pyrazolyl group is rotated around the C-3 - C-3' axis in **4**. At the high energy values the pyrazolyl and ester groups conflict. The smaller peaks show the close contract of 2-H and 4'-H atoms shaded on Figure 1.

The determination of structure of **5** was more difficult because the ^{1}H nmr spectrum of the molecule contains a lot of resonances making difficult the selective irradiation of the different hydrogens during a nOe experiment. The nOe data reveal that there is 6.5% nOe enhancement on one of the 3,4-pyrazolino-methylene hydrogens when the C-3'-CH was irradiated. As the C-3' configuration is the same for both **4** and **5** this result suggest that the 3,4-pyrazolino hydrogens and the C-3'-CH are in close pro-

ximity to each other in space, *i.e.* on the same side of the molecule and the compound **5** has 3*R*,4*S*,3'*S*-configuration (Figure 4).

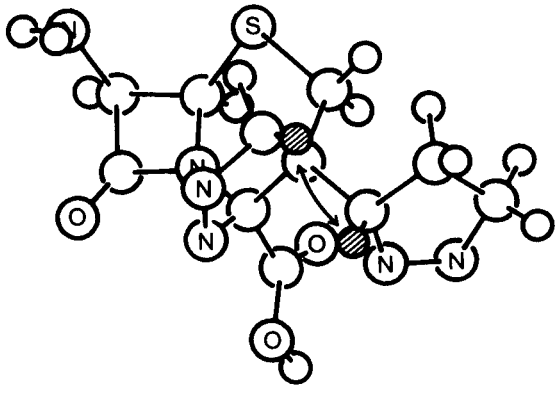


Figure 4. Computer aided design of the structure of the pyrazolinopyrazolilcepham (**5**), which corresponds to the observed nOe between 3'H and 5''-H_{exo}.

Surprisingly, the 1,3-dipolar cycloadditions of the vinylcephalosporin (**1**) with diphenyldiazomethane occurred only after 40 hours reflux in dichloromethane to give two products, the two epimers of **9**. They formed in a ratio 2:1 (**9a**:**9b**). The Δ^3 double bond of the molecule was unaffected in this reaction, neither pyrazolinopyrazolilcephalosporin of type **5** nor compound **10** (Scheme 1) formed.

All of the characterising experiments (nmr, ms, *etc.*) were carried out with the mixture of the epimers. The data from the nOe experiment on the main product (**9a**) is shown in Figure 5. By virtue of these data Structure **b** (Figure 5) is also possible but it was precluded owing to the steric hindrance between the carboxyl group of the cephalosporin nucleus and a phenyl group of the cyclopropane moiety. Thus we can state the structure of the main product (**9a**) is that shown in Figure 5 (Structure **a**) and has the C-1'*S* configuration. The molecule is a result of a less hindered α-face attack of the diazoalkane. The minor product (**9b**) has the C-1'*R* configuration and is formed from the more crowded β-face approach of the diphenyldiazomethane. The most likely structure of this product is shown in Figure 5 (Structure **c**).

The cyclopropylcephalosporins (**9**) did not undergo further cycloadditions with different diazolalkanes to give compounds of type **10**, nor did these types of compounds form from the compound **5** upon heating [8].

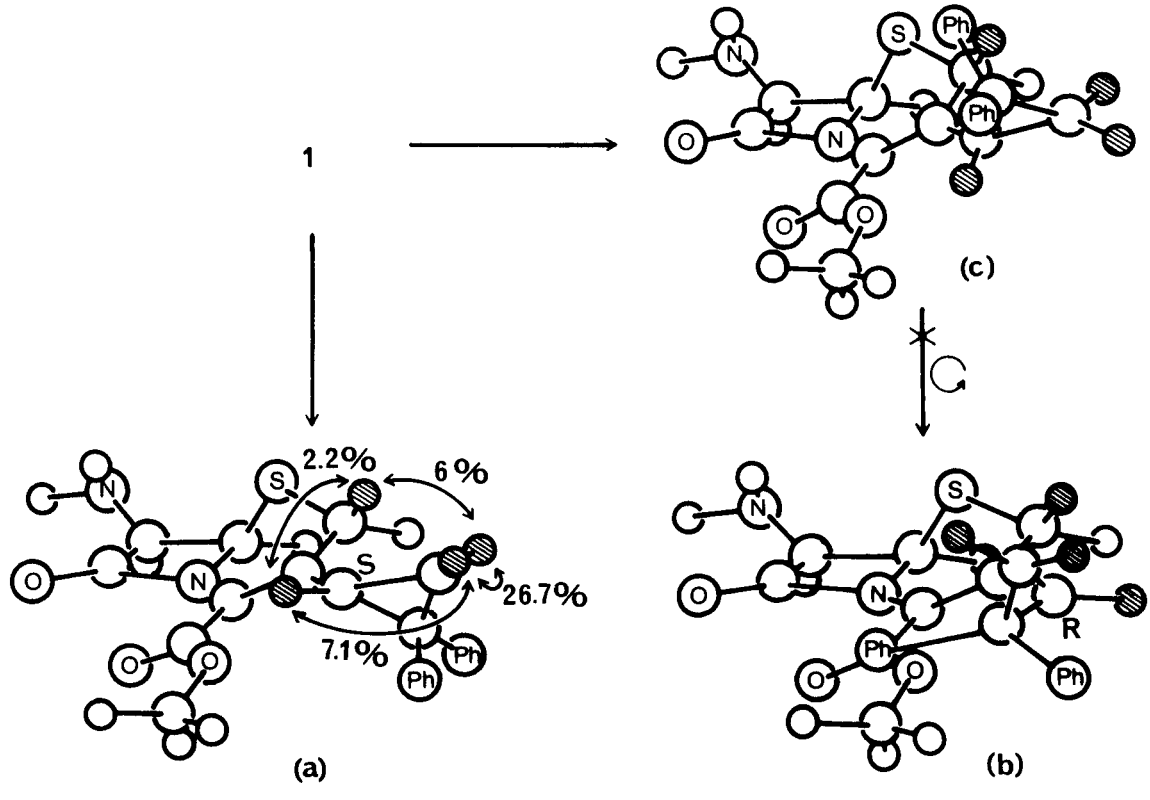


Figure 5. Possible conformations of **9a** and **9b**. In the case of *S* isomer (**a**) (assigned to **9a**) the molecule can adopt the conformation according to the observed nOe values, but not that of the *R* isomer (**b**).

EXPERIMENTAL

Melting points were determined on a PHMK hot plate apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide discs on a Perkin Elmer 283B instrument. The ^1H and ^{13}C nmr spectra were recorded on a Bruker VD 200SY and a Varian Gemini 200 200 MHz spectrometers in deuteriochloroform, perdeuteriobenzene and dimethyl-d_6 sulphoxide solution with tetramethylsilane as internal standard. Ms spectra were obtained on a VG 7035 GC-MS and on a ZAB-1F mass spectrometers. Microanalyses were performed on a Carlo Erba Strumentazone Elemental Analyser, model 1106 interfaced to a Commodore 8296-D computer and in the Microanalysis Laboratory of the Kossuth University of Debrecen. For tlc purposes Merck DC Alurolle Kieselgel 60F 254 was used (uv light, iodine vapour visualisation).

Benzhydryl 7-Phenylacetamido-3-vinyl-3-cephem-4-carboxylate (**1**).

Compound **1** was prepared from 7-aminocephalosporanic acid using literature methods [4] without any modification. Recrystallisation was carried out from a mixture of acetone and water. The physical data are shown in Tables 1 and 2.

Benzhydryl 7-Phenylacetamido-3-vinyl-3-cephem-4-carboxylate 1*S*-(*β*)-Oxide (**2**).

Vinylcephalosporin **1** (2 g, 3.9 mmoles) was dissolved in 200 ml of dichloromethane. The solution was cooled to a maximum 5° and the treated dropwise with 0.8 g (4.2 mmoles, 90% activity) of 3-chloroperbenzoic acid dissolved in 30 ml of dichloromethane. After stirring for 30 minutes the reaction mixture was washed with 10% sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulphate and concentrated to 30 ml and cooled. The white powder precipitated was recrystallized from a mixture of acetone and water (Tables 1 and 2).

Benzhydryl 7-Phenylacetamido-3-(3'-pyrazolyl)-3-cephem-4-carboxylate (**4**) and Benzhydryl 7-Phenylacetamido-3-(3'-pyrazolyl)-3,4-(4'',3''-pyrazolino)cepham-4-carboxylate (**5**).

Compound **1** (1 g, 2 mmoles) was dissolved in 20 ml of dichloromethane and cooled to 0° and a large excess of diazomethane (prepared from 5 g of *N*-nitroso-*N*-methylurea) in 100 ml of diethyl ether was added to this solution. After 1 hour reaction time the solvents were removed in vacuum and the oily residue was chromatographed (Tables 1 and 2).

Benzhydryl 7-Phenylacetamido-3-(3'-pyrazolyl)-3-cephem-4-carboxylate 1*S*-(*β*)-Oxide (**7**).

Method A.

Compound **4** (0.2 g, 0.4 mmole) was dissolved in 30 ml of dichloromethane and cooled to 0°. To this solution 0.14 g (0.44 mmole, 55% activity) of 3-chloroperbenzoic acid in 20 ml of dichloromethane was dropwise added. After stirring for 30 minutes the reaction mixture was washed with 10% sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulphate and cooled. A white powder precipitated.

Method B.

To a solution of vinylcephalosporin sulphoxide **2** (0.1 g, 0.19 mmole) in 20 ml of dichloromethane a large excess of diazomethane (from 2 g *N*-nitroso-*N*-methylurea) in 50 ml of dichloromethane was added. The reaction was followed by tlc. After 4 hours a single product formed which was identical with the product of method A (^1H nmr, tlc) (Tables 1 and 2).

Benzhydryl 7-Phenylacetamido-3-(2',2'-diphenylcyclopropyl)-3-cephem-4-carboxylate (**9a** and **9b**).

Vinylcephalosporin **1** (1 g, 2 mmoles) was dissolved in 20 ml of dichloromethane and 0.6 g (3 mmoles) of diphenyldiazomethane was added. The reaction mixture was refluxed for 40 hours. The solvent was removed and the oily residue chromatographed (Tables 1 and 2).

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REFERENCES AND NOTES

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