Cycloaddition Reactions of Cephalosporin Compounds. XI [1]. 1,3-Dipolar Cycloaddition Reaction of an Exo-2-methylenecephem with Diphenyldiazomethane

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In the 1,3-dipolar cycloaddition reaction of the exo-2-methylenecephem **6** with diphenyldiazomethane the initially formed pyrazolines decompose and spirocyclopropylcephalosporin formation takes place. The structure elucidation with ^1H, ^{13}C, ASIS and NOE nmr methods is also described.

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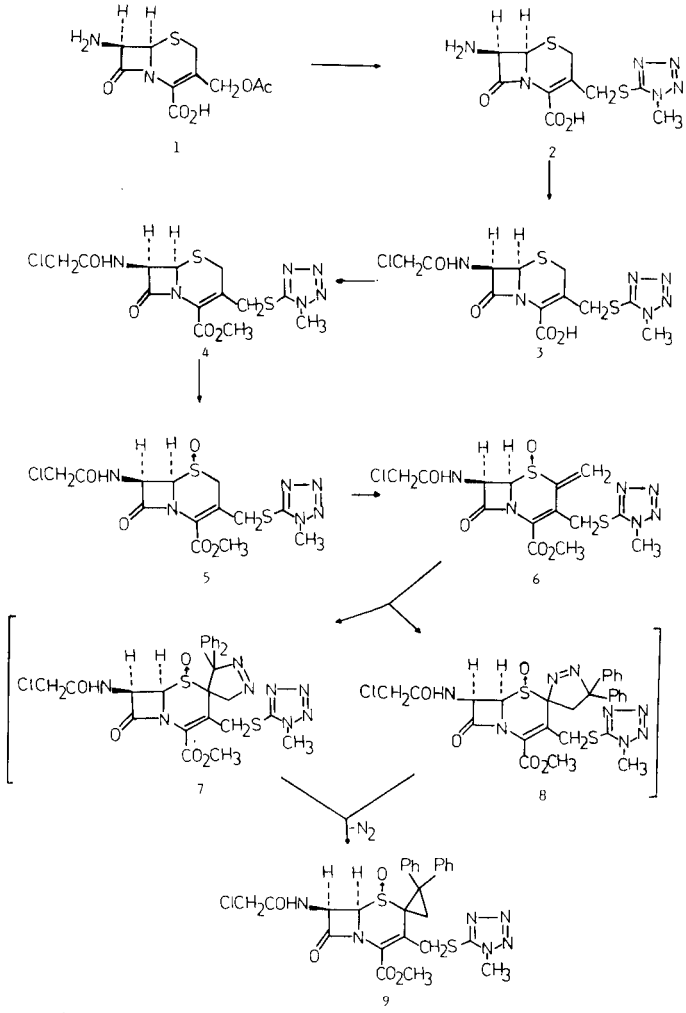
The cycloaddition of diazo compounds to alkenes [2] is a well-known method for the synthesis of pyrazolines. In many cases the cycloadducts are unstable and readily undergo further reactions. Thus in certain cases the initially formed 1-pyrazolines undergo a facile hydrogen shift to give 2-pyrazolines [3]. Elimination of nitrogen from the 1-pyrazolines to give cyclopropanes frequently occurs [4-6].

In our laboratory we study the 1,3-dipolar cycloaddition reactions of cephalosporin derivatives. The Δ^3 double bond of cephems reacts with diazomethane when pyrazoline formation takes place [3b,7]. The stereochemistry of 1-or 2-pyrazolines depend on the reaction conditions and on the substituents of cephalosporins. Bulky diazoalkanes, such as diphenyldiazomethane and ethyl diazoacetate do not give this reaction.

We studied the cycloaddition reactions of exo-2-methylenecephems [8,9] and diazoalkanes [5]. In the case of trichloroethyl 7β-phenylacetamido-2-methylene-3-methyl-3-cephem-4-carboxylate 1*S*(β)-oxide [6] the initially formed pyrazolines decomposed to spirocyclopropyl derivatives. In order to gain further insight into the nature of this reaction we carried out further experiments of this type.

In the reaction of **6** (Scheme 1) with diphenyldiazomethane after 15 minutes two new compounds were formed (tlc) in different amounts. This ratio (9:1) was measured by ^1H nmr of the reaction mixture. The compounds were purified by column chromatography when the minor component rapidly decomposed. The main product was stable. In the ^1H nmr spectra of the components the exomethylene signals (δ 6.45, d) were not observable, and a new ABq signal appeared. The ^{13}C nmr spectra show that the products are cyclopropane derivatives, because the signals of C-3' (Table 1) are in the region of C-CH_2 (δ 21-45) instead of =N-CH_2 (δ 37-58). Thus we can state, that because of the electronic effects in the case of **9a** the initially formed pyrazoline decomposes at once while in the case of **9b** this decomposition takes place only during purification. The nmr data show that the Δ^3 double bond is unreactive in these conditions. Only the less crowded exo double bond undergoes 1,3-dipolar cycloaddition in a *chemospecific reaction.*

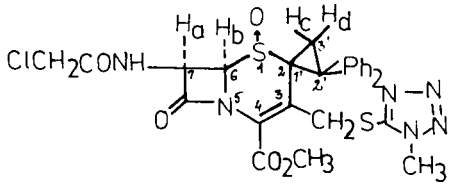
Scheme 1



According to the MO perturbation model [10], electron acceptor-substituted alkenes, as our starting material, **6**, are the dipolarofiles of choice for HOMO (diazoalkane) controlled cycloaddition. The reaction takes place most probably *via* "β-adduct" (**8**), *i.e.* the new carbon-carbon bond forms at the β-carbon of the exomethylenecephalosporin. Therefore in this case the reaction is theoretically *regiospecific.*

Table 1

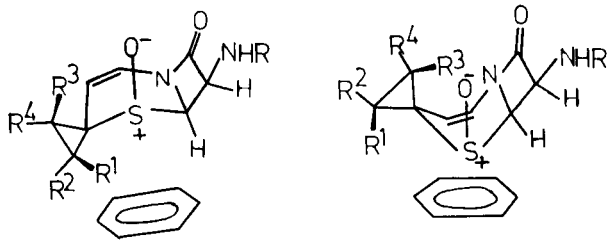
ASIS and ^{13}C NMR Spectral Data of Cyclopropane Derivatives **9a** and **9b**



	Compound	Hydrogens a	b	c	d
δ_{CCDl_3}	**9a**	6.05	4.90	2.90	3.80
	9b	6.05	4.90	3.00	3.85
$\delta_{C_6D_6}$	**9a**	6.10	4.55	3.15	3.95
	9b	6.05	4.15	3.15	3.90
Δ_{ASIS}	**9a**	−0.05	0.35	−0.25	−0.15
	9b	0	0.75	−0.15	−0.05

Carbons	δ (ppm) **9a**	**9b**
C-3′	22.68	27.25
S-CH_2	33.30	33.55
$ClCH_2$	42.05	42.24
C-2′	44.35	57.43
C-2	47.01	59.2
C-7	59.67	59.58
C-6	65.48	65.87
C-3	120.37	123.77
C-4	127.89	128.83

ASIS [11] data of **9a** and **9b** (Table 1) show no significant shifts in the case of cyclopropyl-protons. This means that the products are either in the endo (closed) conformation (Structures **A**, **B**; Figure 1) or in 2*R* configuration and exo (open) conformation (Structure **D**).



I exo (open) II endo (closed)

Structure A II, where $R^1=R^2=H$ $R^3=R^4=Ph$
Structure B II, where $R^1=R^2=Ph$ $R^3=R^4=H$
Structure C I, where $R^1=R^2=H$ $R^3=R^4=Ph$
Structure D I, where $R^1=R^2=Ph$ $R^3=R^4=H$

Figure 1. Orientation of benzene to the cephalosporin S→O dipole and the possible four cyclopropane structures.

The ^1H- $\{^1H\}$ NOE [12] experiments (Figure 2) show no NOE between H6α and cyclopropyl-H_c but between the H6α and the Ph-protons.

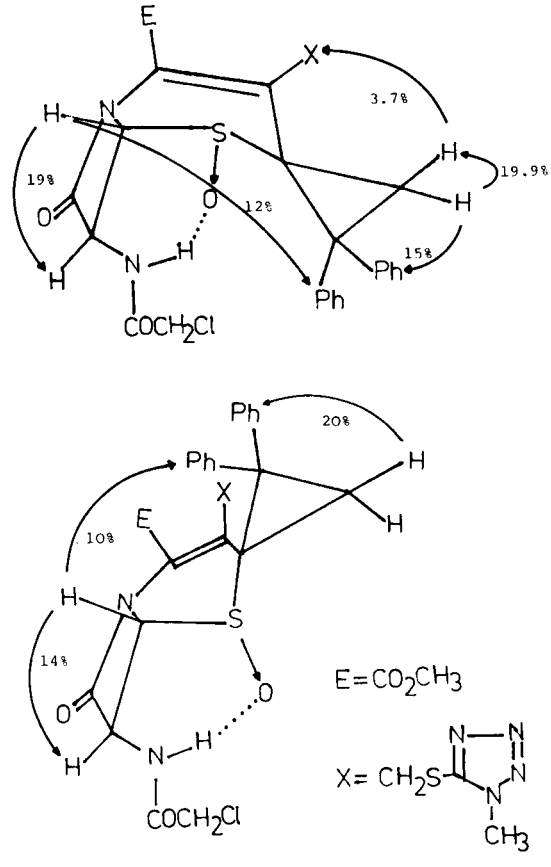


Figure 2. The observed ^1H- $\{^1H\}$ NOE data of cyclopropane derivatives **9a** and **9b**.

These data predict that **9a** is in the 2*R* configuration and exo (open) conformation (Structure **D**, Figure 1) and **9b** in the 2*S* configuration and endo (closed) conformation (Structure **A**). These results fit our other findings [5]. Since the products form in 9:1 ratio, the reaction is *stereoselective*. Compound **9a** was formed by the attack of diphenyldiazomethane on the less crowded α-face while in the case of **9b** the reagent approached the molecule from the more hindered β-face. The latter may have been aided by an interaction between the diazoalkane and the 7β-amide. The endo (closed) conformation of **9b** can be a result of an interaction between the bulky phenyl and *N*-methyltetrazolyl groups.

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 Bruker VP 200SY

Table 2

Physical and Analytical Data for Compounds **2**, **3**, **4**, **5**, **6** and **9**

Compound	mp, °	Yield, %	Molecular formula	Analyses, % Calcd./(Found) N	S	IR, cm^{-1} (β-lactam)	^1H NMR [a], ppm	MS
2	224-226	81	$C_{10}H_{12}N_6O_3S_2$	25.61 (25.44)	19.51 (19.78)	1800	3.65 (ABq, 2H, 2-CH_2), 3.95 (s, 3H, NCH_3), 4.3 (ABq, 2H, CH_2-S), 4.8 (d, 1H, H6), 5.0 (d, 1H, H7) (zwitterionic)	
3	hygroscopic		$C_{12}H_{13}ClN_6O_4S_2$	20.74 (20.43)	15.8 (15.97)	1790	3.7 (ABq, 2H, 2-CH_2), 3.95 (s, 3H, NCH_3), 4.1 (s, 2H, $ClCH_2$), 4.3 (ABq, 2H, CH_2-S), 5.1 (d, 1H, H6), 5.65 (dd, 1H, H7), 9.2 (d, 1H, NH)	
4	78-81	79.4	$C_{13}H_{15}ClN_6O_4S_2$	20.09 (19.6)	15.3 (15.5)	1780	3.7 (ABq, 2H, 2-CH_2), 3.75 (s, 3H, OCH_3), 3.95 (s, 3H, NCH_3), 4.1 (s, 2H, $ClCH_2$), 4.3 (ABq, 2H, CH_2-S), 5.1 (d, 1H, H6), 5.75 (dd, 1H, H7), 9.2 (d, 1H, NH)	
5	169-172	87	$C_{13}H_{15}ClN_6O_5S_2$	19.35 (19.02)	14.75 (14.9)	1785	3.8 (s, 3H, OCH_3), 3.9 (s, 3H, NCH_3), 3.95 (ABq, 2H, 2-CH_2), 4.3 (s, 2H, $ClCH_2$), 4.4 (ABq, 2H, CH_2-S), 4.95 (d, 1H, H6), 5.9 (dd, 1H, H7), 8.6 (d, 1H, NH)	ci: 435 ($M^+ + 1$)
6	138-143	74.2	$C_{14}H_{15}ClN_6O_5S_2$	18.83 (18.46)	14.35 (14.45)	1790	3.8, (s, 3H, OCH_3), 3.95 (s, 3H, NCH_3), 4.3 (s, 2H, $ClCH_2$), 4.5 (ABq, 2H, CH_2-S), 5.1 (d, 1H, H6), 5.95 (dd, 1H, H7), 6.45 (d, 1H, 2-exomethylene), 8.6 (d, 1H, NH)	ei: 446 (M^+)
9a	110-115	59.68	$C_{27}H_{25}ClN_6O_5S_2$	13.72 (13.4)	10.45 (10.02)	1800	3.2 (ABq, 2H, cyclopr-CH_2), 2.95 (s, 2H, CH_2-S), 3.75 (s, 3H, OCH_3), 3.85 (s, 3H, NCH_3), 3.95 (s, 2H, $ClCH_2$), 4.9 (d, 1H, H6), 6.05 (dd, 1H, H7), 7.1-7.2 (m, 10H, aromatic) 7.7 (d, 1H, NH)	ei: 612 (M^+) Fab: 613 ($M^+ + 1$)
9b	103-107	6.45	$C_{27}H_{25}ClN_6O_5S_2$	13.72 (13.38)	10.45 (10.52)	1798	3.4 (ABq, 2H, cyclopr-CH_2), 3.02 (s, 2H, CH_2-S), 3.9 (s, 3H, OCH_3), 3.95 (s, 3H, NCH_3), 4.02 (s, 2H, $ClCH_2$), 4.9 (d, 1H, H6), 6.05 (dd, 1H, H7), 7.05-7.3 (m, 10H, aromatic), 7.8 (d, 1H, NH)	

[a] In the case of **2**, **3**, **4** the solvent was dimethyl-d_6 sulfoxide-d_6 and in the case of **5**, **6**, **9** the solvent was deuteriochloroform.

200 MHz spectrometer in deuteriochloroform, perdeuteriobenzene and dimethyl sulfoxide-d_6 solutions, with tetramethylsilane as internal standard. Mass spectra were obtained on a VG 7035 GC-MS and on a AEI MS 902 mass spectrometer. For tlc purposes Merck DC Alurolle Kieselgel 60F 254 was used (uv light, iodine vapour visualisation).

7-Amino-3-(1-methyltetrazol-5-yl-thiomethyl)-3-cephem-4-carboxylic Acid (**2**) [13].

A suspension of 10.88 g (40 mmoles) of 7-aminocephalosporanic acid (**1**) in 100 ml of acetic acid was treated with 4.6 g (41 mmoles) of 1-methyl-5-mercaptotetrazole and 23.04 g (15.5 ml) of methanesulfonic acid, stirred at 50° for 2.5 hours, cooled and added to 27 ml of water. The mixture was adjusted to *p*H 4.0 with ammonia solution and the precipitate filtered off, washed and dried. The physical data are shown in Table 2.

7-Chloroacetamido-3-(1-methyltetrazol-5-yl-thiomethyl)-3-cephem-4-carboxylic Acid (**3**).

Compound **2** (20.27 g, 50 mmoles) was transferred into a three-necked flask, dissolved in an ice cold solution of sodium hydrogencarbonate (10.6 g) in 335 ml of water and of acetone. The mixture was treated dropwise with a solution of 4.5 ml of chloroacetyl chloride in 30 ml of acetone. After stirring for 3 hours the acetone was removed under reduced pressure. The aqueous solution was then poured into a separatory funnel. Two hundred ml of ethyl acetate was added to this solution and acidified to *p*H 2.5-3.0 with 40% phosphoric acid. After shaking the aqueous layer was removed, than extracted with further 100 ml of ethyl acetate. The combined organic layer was washed with water,

dried over anhydrous magnesium sulphate and evaporated in vacuum (Table 2).

Methyl 7-Chloroacetamido-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate (**4**).

Compound **3** (20 g, 50 mmoles) was dissolved in 350 ml of dichloromethane and treated with an ethereal solution of diazomethane until the yellow color of diazomethane remained unchanged in the reaction mixture. The solution then was treated with a few drops of acetic acid to remove excess diazo compound, washed with 10% sodium hydrogen carbonate solution and dried over anhydrous magnesium sulphate. The solvents were removed in vacuum and the ester was recrystallized from a mixture of methanol and ether (Table 2).

Methyl 7-Chloroacetamido-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate 1*S*-(*β*)-Oxide (**5**).

The ester 4 (8.4 g, 20 mmoles) was dissolved in 100 ml of dichloromethane. The solution was cooled to a maximum 5° and then treated dropwise with 3.45 g (21 mmoles, 90% activity) of 3-chloroperbenzoic acid dissolved in 50 ml of dichloromethane. The reaction mixture was washed with 10% sodium hydrogen carbonate solution and water, dried over anhydrous magnesium sulphate and evaporated. During evaporation a white powder precipitated (Table 2).

Methyl 7-Chloroacetamido-2-methylene-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate 1*S*-(*β*)-Oxide (**6**).

Compound **5** (4 g, 9.2 mmoles) was dissolved in 250 ml of hot dichloromethane. To this solution 1.15 g (10.5 mmoles) of diethylamine hydrochloride and 1 g of *p*-formaldehyde were added, and the mixture was refluxed for 24 hours. The reaction mixture was concentrated to 25 ml and cooled. A yellowish powder slowly precipitated (Table 2).

Methyl 7-Chloroacetamido-2-(2',2'-diphenylspirocyclopropyl)-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate 1*S*-(*β*)-Oxide (**9**).

Compound **6** (0.45 g, 1 mmole) was dissolved in 50 ml of dichloromethane, 0.2 g (1.1 mmoles) of diphenyl diazomethane was added to this solution. The reaction mixture was kept at room temperature for a half an hour then the solvent was evaporated and the oily residue was chromatographed.

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