On the Preparation of 2-Substituted Cephalosporins

Part 2

Diels–Alder and 1,3-Dipolar Cycloadditions of 2-Crotonoyl (=(2*E*)-But-2-enoyl), 2-Sorboyl (=(2*E*,4*E*)-Hexa-2,4-dienoyl), and 2-Cinnamoyl (=(2*E*)-3-Phenylprop-2-enoyl) Substituted Deacetoxycephalosporanate 1-Oxides

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Cephalosporin sulfoxides **1** and **2** containing an enone- or dienone-type moiety at position 2 were treated with 2,3-dimethylbuta-1,3-diene or diethyl azodicarboxylate to synthesize, in *Diels–Alder* reactions, the new cephalosporin derivatives **4** and **5** with a cyclic substituent (*Scheme 1*). Under the same conditions, ethyl diazoacetate and diazomethane reacted differently: while reactions of **1** and **3** with the former lead to compounds **7**–**10** corresponding to the 1,3-dipolar cycloaddition route (*Scheme 2*), diazomethane produced only enol ethers **12** and **13**, respectively (*Scheme 3*). This difference could be rationalized by assuming two different reaction pathways: an orbital-symmetry-controlled concerted cycloaddition and an ionic one.

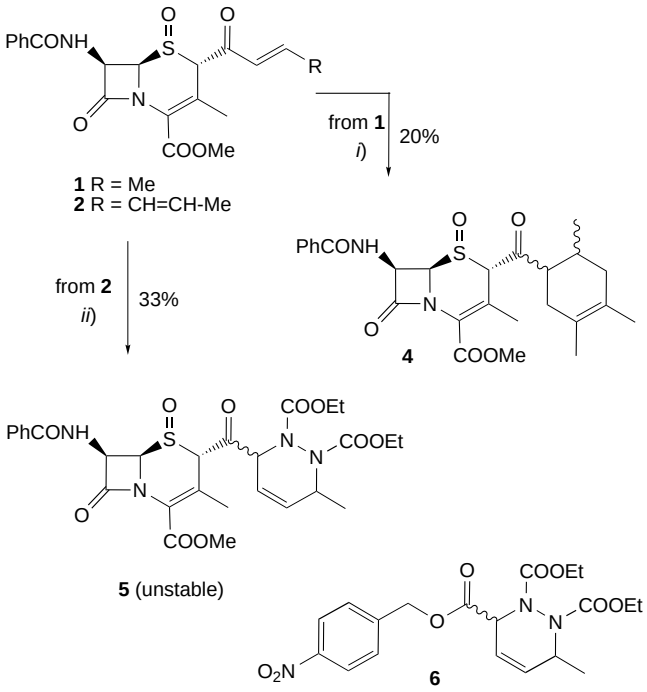
Introduction. – In the late 80's, several cephalosporin derivatives were found to possess human leukocyte elastase (HLE) enzyme inhibitor activity [1]. The systematic investigations were extended to the 2-substituted cephems, showing that these derivatives could be particularly potent inhibitors of HLE. The 2-substituted cephalosporins are generally insignificant as antimicrobial agents and, therefore, they were not well investigated in earlier decades. The results of the biological tests drew more attention to these modifications, since both the higher oxidation state of the S-atom and the C(2) substitution of the cephem ring system led to new compounds with enhanced HLE-enzyme-inhibitory properties.

Earlier, we described the syntheses of new 2-substituted cephalosporins *via* lithium diisopropylamide generated anions of cephalosporin sulfoxides [2]. This method was optimized and used to prepare cephem derivatives having an α,β-unsaturated ketone moiety at C(2). These compounds can be expected to be versatile intermediates for the syntheses of further cephems *via* cycloadditions of the unsaturated side chain. Unfortunately, most of these reactions proved to be sluggish and showed extensive degradations of the cephem ring system as well, and some of these derivatives were found to exhibit unexpected behaviors. Herein, we report our investigations on these reactions with the aim to synthesize new cephalosporins containing carbocyclic and heterocyclic substituents at C(2) and some theoretical considerations to explain the unexpected results.

Results and Discussion. – *Syntheses.* Our initial goal was to react cephems bearing at C(2) a sorboyl (=(2*E*,4*E*)-hexa-2,4-dienoyl), cinnamoyl (=(2*E*)-3-phenylprop-2-

enoyl), or crotonoyl (=(2*E*)-but-2-enoyl) substituent as dienes or dienophiles in *Diels–Alder* and 1,3-dipolar cycloaddition reactions to obtain new 2-substituted cephalosporins. In the *Diels–Alder* reactions of either normal or reverse electron demand, these cephems showed low reactivity. On reaction of **1** with 2,3-dimethylbuta-1,3-diene (*Scheme 1*), **4** was obtained in only very low yield as the mixture of the two (*cis*-3,4,6-trimethylcyclohex-3-en-1-yl)-substituted diastereoisomers, according to the general rules of thermal *Diels–Alder* reactions. By increasing the pressure by carrying out the reaction in a sealed tube at elevated temperature, and/or in the presence of $LiClO_4$ as a catalyst, the yield could be increased to *ca.* 20%. The cephem derivative **2**, as a diene, was found to be similarly inert in *Diels–Alder* reactions. It failed to react with several dienophiles, *e.g.*, vinyl *tert*-butyl ether, vinyl butyl ether, vinyl acetate, or 3,4-dihydrofuran.

Scheme 1



i) 2,3-Dimethylbuta-1,3-diene, toluene 80°, $LiClO_4$, *ii*) Diethyl azodicarboxylate, toluene, r.t.

Scheradsky et al. [3] reported the intramolecular *Diels–Alder* reaction of similar dienone systems and compounds with a *N*,*N*′-diacyldiazene moiety generated *in situ* in boiling toluene. Reaction of **2** with diethyl azodicarboxylate (=diethyl diazenedicarboxylate; DEAD) under the same conditions resulted in complex mixtures only, whereas at room temperature and in the presence of silica gel as catalyst, the cycloadduct **5** was obtained as the mixture of *trans* diastereoisomers. Its structure was

established by NMR spectroscopy with **6** as reference compound[1]). *Fig. 1* shows the characteristic ^{1}H-NMR features of the newly formed ring. The spectra clearly reveal that the peaks of the protons of the unsaturated side chain at C(2) of **2** have disappeared and, in turn, signals of H−C(1′) to H−C(4′) of the newly formed heterocyclic ring have emerged. Unfortunately, this cycloadduct turned out to be unstable, and it degraded slowly on standing in the NMR tube.

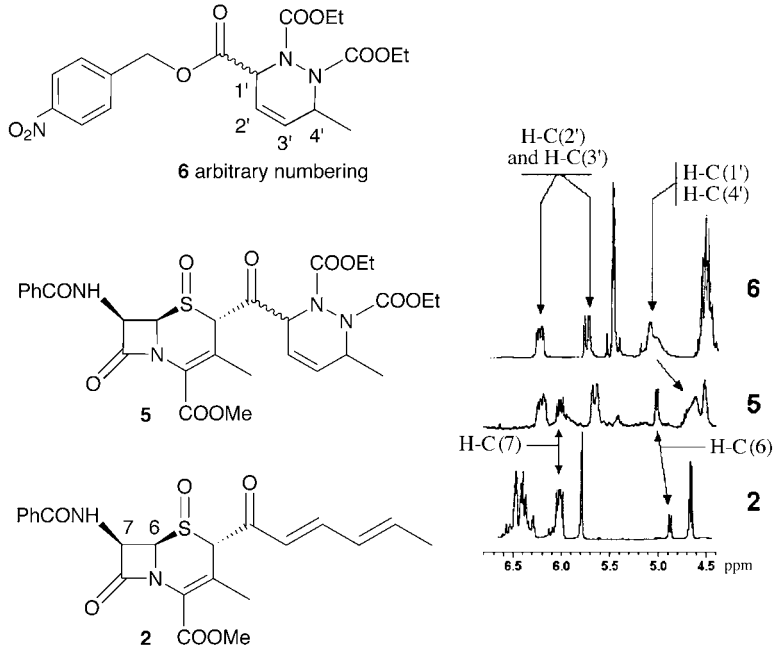


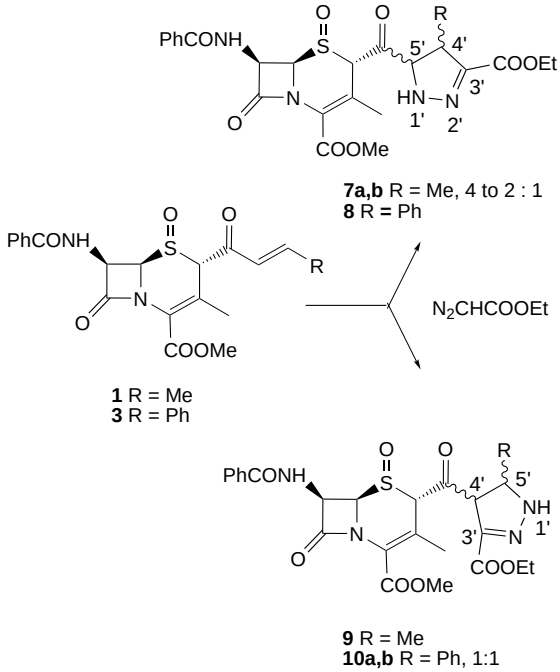
Fig. 1. *Comparison of the ^{1}H-NMR spectra of relevant protons of* **2**, **5**, *and* **6**

The non-regioselective 1,3-dipolar cycloaddition reactions of 2-crotonoyl- and 2-cinnamoylcephems **1** and **3** with ethyl diazoacetate provided two new regioisomeric cephem derivatives in each case, *i.e.*, the (5-phenyl-1*H*-pyrazol-4-yl)- and (4-phenyl-1*H*-pyrazol-5-)-substituted isomers **10** and **8**, respectively, or the analogous 5-methyl and 4-methyl isomers **9** and **7**, respectively (*Scheme 2*). Theoretically, all of these compounds have two *cis* and two *trans* stereoisomers; in fact, only the *trans* isomers were formed, as expected and in accordance with the NMR spectra. Both *trans* isomers were isolated in the case of **7** and **10**, but one only in case of **8** and **9**.

In all of these trials, we obtained complex reaction mixtures, and the purification and separation of the isomers needed column chromatography in each case. The regioisomer mixtures **7**/**9** and **8**/**10** could be separated, but not all of the stereoisomers. The phenyl derivatives **10a**,**b** were successfully separated by column chromatography and their ratio (1:1) determined from the yields of the isolated material. The methyl derivatives **7a**,**b** could not be fully separated by column chromatography (only one of

[1]) Compound **6** was easily prepared by reacting 4-nitrobenzyl sorbate with DEAD in boiling toluene.

Scheme 2



the *trans* isomers was obtained in pure form), their ratio was 2 to 4 : 1, based on the NMR data, depending upon the reaction conditions (room temp. *vs.* 60°). Only one of the *trans* isomers of **8** and **9** were obtained.

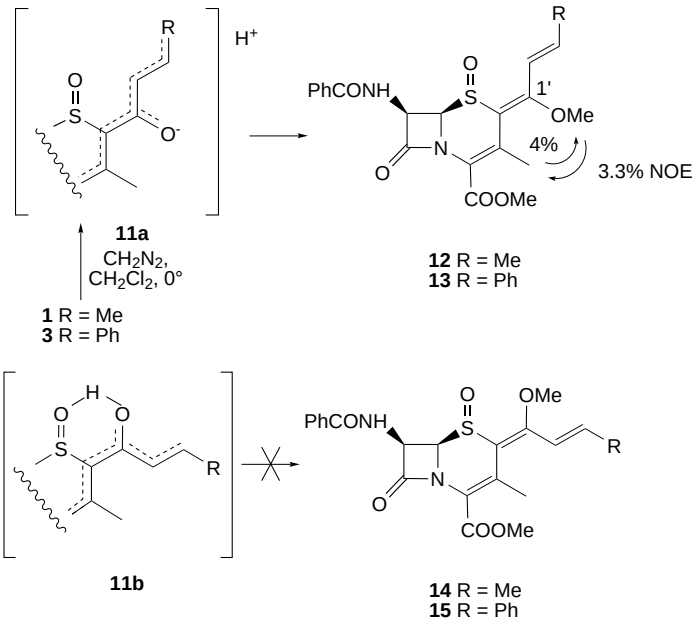
To synthesize further heterocyclic derivatives, the 2-cinnamoyl-, and 2-crotonoyl-cephems **1** and **3** were treated with diazomethane (*Scheme 3*). Similar cycloadditions have already been studied in the case of 2-methylene [1a][4] and 3-vinylcephalosporins [5]. It is a general experience that the primary products of this type of reaction are 3*H*-4,5-dihydropyrazoles which can easily undergo spontaneous N_2 elimination to give spirocyclopropanes. To avoid such decompositions, we carried out these reactions at 0° and paid attention to keep the temperature of the reaction mixture below 10° during workup. Surprisingly, neither the expected dihydropyrazoles nor the spirocyclopropane derivatives could be isolated in our trials, but the enol ethers **12** and **13** were obtained (*Scheme 3*).

The configuration of the side chain of the product **12** was examined by ^{1}H,^{1}H-NOE experiments. The MeO–C(1′) group exhibited NOE interactions with Me–C(3) (see *Scheme 3*), thus, the (*E*) isomers **12** and **13** were formed selectively in the reaction.

Two questions arise from this reaction: *a*) why does methylation take place instead of 1,3-dipolar cycloaddition when diazomethane is used; *b*) why are the (*E*) isomers formed selectively during methylation?

Methylation vs. *Cycloaddition*. The difference in the reactions of the cephems with diazomethane and ethyl diazoacetate was somewhat unexpected (*Scheme 3 vs. 2*): although the use of diazomethane for the methylation of enolizable ketones is well-

Scheme 3



known, enolizable α,β-enones (with similar enone substructure as in **1** and **3**) have been reported to give heterocyclic or cyclopropyl compounds or β-methyl-substituted ketones [6]. This prompted us to seek a rational explanation. For this purpose, we carried out AM1 calculations for **1**, **3**, diazomethane, and ethyl diazoacetate to determine the energies of their frontier molecular orbitals (*Fig. 2*). The differences in energy of the LUMO (cephems) and the HOMO (diazo compounds) are between 7.7 and 8.8 eV, whereas the differences in energy of the HOMO (cephems) and the LUMO (diazo compounds) are between 8.9 and 10.0 eV. This suggests that the former interactions with reverse electron demand are preferred.

To interpret the results, two reaction pathways must be assumed: an ionic one that leads to the enol-ether product (*Scheme 3*) and another one controlled by orbital symmetry and leading to the cycloadducts (*Scheme 2*). The reaction of ethyl diazoacetate with the cephems follows the orbital-symmetry-controlled pathway, while, in the reaction with diazomethane, the ionic pathway is dominant. Since the HOMO energy of diazomethane is higher than that of ethyl diazoacetate, the orbital-symmetry-controlled pathway is expected to be more favorable for diazomethane from an energetic point of view, resulting in a faster reaction. In fact, diazomethane reacted with the cephems *via* the ionic mechanism. The reason for this can be attributed to the differences in the acidic features of the reactants: because of the higher HOMO energy, diazomethane is a stronger *Lewis* base than ethyl diazoacetate; therefore, it can deprotonate **1** and **3** to give **11a** (anionic pathway).

*Formation of the (*E*)-Enol Ethers.* A plausible explanation of the formation of the (*E*)-isomer would be a possible intramolecular H-bridge between the enol H-atom and

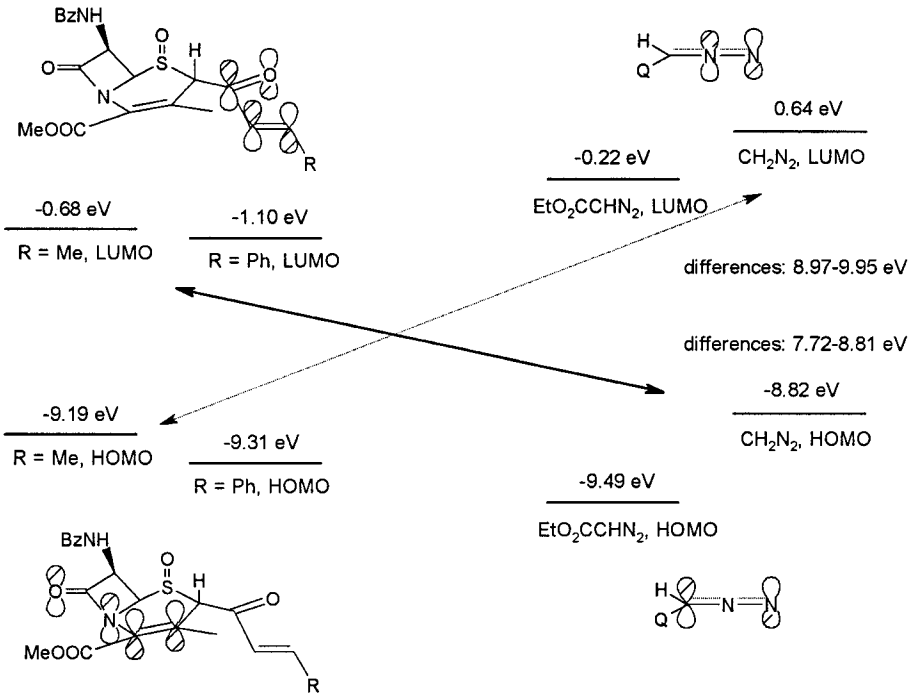


Fig. 2. *AM1 Calculated HOMO and LUMO energies of* **1**, **3**, *diazomethane, and ethyl diazoacetate*

the sulfoxide O-atom (see **11b**). As it is a general observation that protons that take part in intramolecular H-bonds are less reactive than free ones, the isolated (*E*)-isomers **12** and **13** would be the products of a kinetically controlled reaction (*via* **11a**). However, molecular modelling shows that the distance between the S-oxide O-atom and the enolic OH is well beyond the range of H-bonds (*Fig. 3,a*). Geometry optimization of **1** (semiempirical MOPAC method based on the MNDO/d Hamiltonian) revealed that the arrangements of the 2α-positioned side chain are charac-

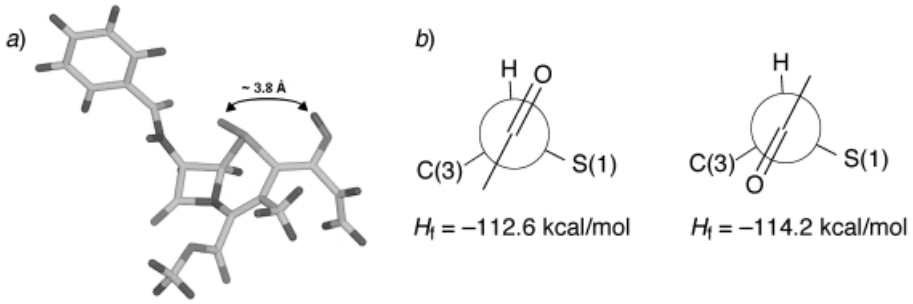


Fig. 3. a*) MNDO/d-Optimized geometry of* **11b** (the possible minimal distance between the sulfoxide O and the enol H is *ca.* 3.8 Å). b*) The two stable conformations of the side chain at C(2) of* **1** *and the corresponding heats of formation.*

terized by two distinct energy minima differing by only 1.6 kcal/mol. Thus, the conformation with a nearly *anti*-periplanar arrangement of H–C(2) and the side-chain carbonyl group has a slight preference over the *gauche*-like one. Reaction of the former conformer with CH_2N_2 leads to the (*E*)-isomer and can explain the experimental preference for **12** and **13**.

This work was funded by the grant of the *Hungarian National Science Fund*, OTKA T 34298.

Experimental Part

General. All reactions were followed by TLC (*Merck* silica gel *60* F_{254}). Column chromatography (CC): *Merck* silica gel *60*. M.p.: *Kofler*-type hot-stage apparatus, uncorrected. IR Spectra: *Perkin-Elmer 1600*-FT-IR spectrophotometer, KBr pellets; in cm^{-1}. ^{1}H-NMR Spectra: *Bruker WP-SY-200* instrument; ^{1}H at 200 MHz, ^{13}C at 50 MHz; $SiMe_4$ as internal standard; *J* values in Hz, chemical shifts δ in ppm. Elemental analyses: *Carlo-Erba EA-1108* instrument. The AM1 and MNDO calculations were carried out by Hyperchem 6.03 for Windows (*Hypercube, Inc.*) program.

*Methyl (2S,6R,7R)-7-Benzamido-3-*C*-deacetoxy-2-{[(1RS,6RS)-3,4,6-trimethylcyclohex-3-enyl]carbonyl}-cephalosporanate 1-Oxide* (= *Methyl (4S,6R,7R)-7-(Benzoylamino)-3-Methyl-8-oxo-4-{[(1RS,6RS)-3,4,6-trimethylcyclohex-3-enyl]carbonyl}-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 5-Oxide*; **4**). A mixture of **1** (400 mg), $LiClO_4$ (40 mg), and 2,3-dimethylbuta-1,3-diene (4.3 ml) was heated in toluene (30 ml) at 80° in a closed *Teflon* bomb-tube for 2 h. The mixture was evaporated and the residue purified by CC (toluene/AcOEt 3:1) and recrystallization from ^{i}PrOH: **4** (20%). M.p. 209–213° (dec.). IR (KBr): 1792, 1728, 1646, 1522. ^{1}H-NMR ((D_6)DMSO): 0.77 (*d*, *J* = 5.7, Me–C(6′)); 1.57 (*s*, Me–C(3′), Me–C(4′)); 1.79–2.10 (*m*, 2 H–C(2′), 2 H–C(5′)); 1.98 (*s*, Me–C(3)); 2.70–2.90 (*m*, H–C(6′)); 3.00–3.20 (*m*, H–C(1′)); 3.84 (*s*, COOMe); 4.62 (*d*, *J* = 4.6, H–C(6)); 5.76 (*s*, H–C(2)); 6.03 (*dd*, *J* = 4.6, 7.6, H–C(7)); 7.46–7.63 (*m*, 3 arom. H); 7.81–7.87 (*m*, 2 arom. H); 8.67 (*d*, *J* = 7.6, NH). ^{13}C-NMR ($CDCl_3$): 18.5, 18.6, 19.0, 19.16 (4 Me); 31.1 (C(6′)); 33.3 (CH_2); 39.5 (CH_2); 52.6 (C(6)); 53.7 (C(1′)); 59.6 (C(7)); 64.7 (C(2)); 73.6 (COO*Me*); 120.0, 122.9, 123.3, 124.6 (unsat. quat. C); 127.7, 128.5 (2 arom. CH); 132.1 (1 arom. CH); 132.8 (1 arom. quat. C); 161.7, 162.7, 166.6, 206.1 (4 CO). Anal. calc. for $C_{26}H_{30}N_2O_6S$: C 62.63, H 6.06, N 5.62, S 6.43; found: C 62.36, H 6.27, N 5.53, S 6.11.

*Methyl (2S,6R,7R)-7-Benzamido-3-*C*-deacetoxy-2-{[(3RS,6RS)-1,2-bis(ethoxycarbonyl)-1,2,3,6-tetrahydro-6-methyl-pyridazin-3-yl]carbonyl}cephalosporanate 1-Oxide* (= *Diethyl (3RS)-3-{{[(4S,6R,7R)-7-(Benzoylamino)-2-(methoxycarbonyl)-3-methyl-5-oxido-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-4-yl}carbonyl}-3,6-dihydro-6-methylpyridazine-1,2-dicarboxylate*; **5**). A mixture of **2** (84 mg, 0.2 mmol), diethyl azodicarboxylate (DEAD; 1 ml, 6.4 mmol) and SiO_2 (silica gel *60*, 0.063–0.200 mm; 2 g) was stirred in toluene (10 ml) for 24 h at r.t. After completion of the reaction, SiO_2 (4 g) suspended in Et_2O (40 ml) was added, and the suspension was filtered. The filter cake was rinsed with AcOEt (3 × 50 ml), the org. phase evaporated, and the solid residue dried *i.v.*. 39 mg of **5**, which slowly decomposed even during the NMR measurements. Therefore, no correct elemental analysis could be obtained. ^{1}H-NMR ((D_6)DMSO): 1.00–1.30 (*m*, 2 Me); 3.20–3.50 (*s*, 2 Me); 3.80 (*s*, MeO); 4.01–4.20 (*m*, 2 CH_2);4.51 (*s*, H–C(2)); 4.60–4.80 (*m*, 2 H); 5.01 (*d*, *J* = 4.5, H–C(6)); 5.64 (*d*, *J* = 8.0, 1 H); 6.01 (*dd*, *J* = 8.1, 4.5, H–C(7)); 6.10–6.30 (*m*, 1 H); 7.30–7.60 (*m*, 3 arom. H); 7.70–8.00 (*m*, 2 arom. H); 8.46 (*d*, *J* = 8.1, NH).

1,2-Diethyl 3-(4-Nitrobenzyl) (3RS,6RS)-3,6-Dihydro-6-methylpyridazine-1,2,3-tricarboxylate (**6**). A soln. of 4-nitrobenzyl sorbate (=4-nitrobenzyl (2*E*,4*E*)-hexa-2,4-dienoate; 0.5 g, 2.4 mmol) and DEAD (0.5 ml) in toluene (10 ml) was refluxed for 29 h and monitored by TLC. After the reaction was complete, the mixture was evaporated and the residue purified by CC (toluene/AcOEt 5:1): **6** (0.87 g, 87%). Clear oily material, which crystallized spontaneously within a few weeks. M.p. 55–59°. IR (KBr): 1749, 1714, 1522, 1380. ^{1}H-NMR ($CDCl_3$): 1.16 (*t*, *J* = 7.0, 2 Me); 1.34 (*t*, *J* = 6.7, Me); 3.99–4.20 (*m*, 4 H); 4.71–4.89 (*m*, 2 H); 5.15–5.30 (*m*, 2 H); 5.54 (*dd*, *J* = 10.0, 1.7, 1 H); 6.09 (*ddd*, *J* = 1.7, 10.0, 5.0, 1 H); 7.47 (*d*, *J* = 8.7, 2 H); 8.12 (*d*, *J* = 8.7, 2 H). ^{13}C-NMR ($CDCl_3$): 14.1, 17.6 (2 *Me*CH_2O); 50.9, 57.4 (2 CH); 62.3, 62.7, 65.4 (3 CH_2); 119.9, 134.0 (unsat. CH); 123.5, 128.0 (arom. CH); 142.7 (arom. quat. C); 147.4, 156.2, 167.9 (3 CO).

Reaction of **1** *or* **3** *with Ethyl Diazoacetate*. To a soln. of **3** or **1** (2 g) in $CHCl_3$ was added ethyl diazoacetate (2.5 ml, 6 equiv). The mixture was heated under reflux. When the reaction was complete (TLC monitoring), the solvent was evaporated and the mixture purified by CC (toluene/AcOEt 5:1): **8**/**10** or **7a**,**b**/**9**, resp.

*Methyl (2S,6R,7R)-7-Benzamido-3-*C*-deacetoxy-2-{[(4RS,5SR)-3-(ethoxycarbonyl)-4,5-dihydro-4-methyl-1*H*-pyrazol-5-yl]carbonyl}cephalosporanate 1-Oxide* (= *Methyl (4S,6R,7R)-7-(Benzoylamino)-4-{[(4RS,5SR)-*

*3-(ethoxycarbonyl)-4,5-dihydro-4-methyl-1*H*-pyrazol-5-yl]carbonyl}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 5-Oxide*; **7a**): major *trans* isomer. Yield 20%. M.p. 137–139°. IR (KBr): 1784, 1734, 1684, 1522. ^{1}H-NMR ($CDCl_3$): 1.24–1.34 (*m*, $COOCH_2$*Me*, Me–C(4′)); 2.11 (*s*, Me–C(3)); 3.46–3.54 (*m*, H–C(4′)); 3.90 (*s*, COOMe); 4.16–4.23 (*m*, $COOCH_2$Me, H–C(5′)); 4.99 (*d*, *J* = 4.6, H–C(6)); 5.99 (*s*, H–C(2)); 6.30 (*dd*, *J* = 4.6, 9.7, H–C(7)); 7.40–7.44 (*m*, 3 arom. H, CONH); 7.70–7.85 (*m*, 2 arom. H); 8.30 (*s*, H–N(1′)). ^{13}C-NMR ($CDCl_3$): 14.0 ($COOCH_2$*Me*); 17.7 (*Me*–C(4′)); 19.0 (*Me*–C(3)); 40.5 (C(4′)); 52.6 (COO*Me*); 58.7 (C(7)); 62.2 ($COOCH_2$Me); 65.4 (C(6)); 68.0 (C(2)); 70.3 (C(5′)); 123.2 (C(3)); 123.6 (C(4)); 127.3 (2 arom. CH); 128.6 (2 arom. CH); 132.3 (1 arom. CH); 132.4 (arom. quat. C); 150.0 (C(3′)); 161.6, 163.5, 167.0, 170.0, 183.5 (5 CO). Anal. calc. for $C_{24}H_{26}N_4O_8S$ (530.56): C 54.33, H 4.94, N 10.56, S 6.04; found: C 54.82, H 4.83, N 10.96, S 5.81.

*Methyl (2*S*,6*R*,7*R*)-7-Benzamido-3-*C*-deacetoxy-2-{[(4*RS*,5*SR*)-3-(ethoxycarbonyl)-4,5-dihydro-4-phenyl-1*H*-pyrazol-5-yl]carbonyl}cephalosporanate 1-Oxide* (= *Methyl (4*S*,6*R*,7*R*)-7-(Benzoylamino)-4-{[(4-*RS*,5*SR*)-3-(ethoxycarbonyl)-4,5-dihydro-4-phenyl-1*H*-pyrazol-5-yl]carbonyl}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 5-Oxide*; **8**): Yield 10%. M.p. 197–199°. IR (KBr): 1733, 1652, 1456, 1378. ^{1}H-NMR ((D_6)DMSO): 1.21 (*t*, *J* = 7.1, $COOCH_2$*Me*); 1.87 (*s*, Me–C(3)); 3.79 (*s*, COOMe); 4.11–4.23 (*m*, $COOCH_2$Me); 4.53 (*d*, *J* = 6.4, H–C(4′)); 4.67 (*d*, *J* = 6.4, H–C(5′)); 4.77 (*d*, *J* = 4.6, H–C(6)); 5.86 (*s*, H–C(2)); 6.05 (*dd*, *J* = 7.6, 4.6, H–C(7)); 7.08–7.12 (*m*, 2 arom. H); 7.24–7.73 (*m*, 3 arom. H); 7.43–7.63 (*m*, 3 arom. H); 7.81–7.85 (*m*, 2 arom. H); 8.59 (*d*, *J* = 7.6, NHCO); 10.49 (*s*, H–N(1′)). ^{13}C-NMR ($CDCl_3$): 14.1 ($COOCH_2$*Me*); 19.0 (Me–C(3)); 50.9 (C(4′)); 52.6 (COO*Me*); 58.9 (C(7)); 62.6 ($COOCH_2$Me); 65.4 (C(6)); 66.0 (C(2)); 71.5 (C(5′)); 122.9 (C(3)); 123.7 (C(4)); 126.7, 127.4, 128.7, 129.3, 128.2, 132.4 (arom. CH); 132.6, 138.8 (arom. quat. C); 149.9 (C(3′)); 161.6, 163.4, 167.0, 169.6, 183.5 (5 CO). Anal. calc. for $C_{29}H_{28}N_4O_8S$ (592.63): C 58.78, H 4.76, N 9.45, S 5.41; found: C 58.97, H 4.71, N 9.42, S 5.90.

*Methyl (2*S*,6*R*,7*R*)-7-Benzamido-3-*C*-deacetoxy-2-{[(4*RS*,5*RS*)-3-(ethoxycarbonyl)-4,5-dihydro-5-methyl-1*H*-pyrazol-4-yl]carbonyl}cephalosporanate 1-Oxide* (= *Methyl (4*S*,6*R*,7*R*)-7-(Benzoylamino)-4-{[(4*RS*,5*RS*)-3-(ethoxycarbonyl)-4,5-dihydro-5-methyl-1*H*-pyrazol-4-yl]carbonyl}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 5-Oxide*; **9**): Yield 35%. Yellow viscous oil. IR (film): 1789, 1732, 1652, 1520. ^{1}H-NMR ($CDCl_3$): 1.23–1.38 (*m*, $COOCH_2$*Me*, Me–C(4′)); 2.17 (*s*, Me–C(3)); 3.90 (*s*, COOMe); 4.15–4.23 (*m*, $COOCH_2$Me, H–C(5′)); 4.68–4.80 (*m*, H–C(4′)); 4.93 (*d*, *J* = 4.7, H–C(6)); 5.95 (*s*, H–C(2)); 6.31 (*dd*, *J* = 4.7, 9.5, H–C(7)); 7.43–7.56 (*m*, 3 arom. H); 7.79–7.83 (*m*, 1 arom. H, NHCO); 8.20 (*s*, H–N(1′)). Anal. calc. for $C_{24}H_{26}N_4O_8S$ (530.56): C 54.33, H 4.94, N 10.56, S 6.04; found: C 54.95, H 4.67, N 10.76, S 5.98.

*Methyl (2*S*,6*R*,7*R*)-7-Benzamido-3-*C*-deacetoxy-2-{[(4*RS*,5*RS*)-3-(ethoxycarbonyl)-4,5-dihydro-5-phenyl-1*H*-pyrazol-4-yl]carbonyl}cephalosporanate 1-Oxide* (= *Methyl (4*S*,5*R*,6*R*)-7-(Benzoylamino)-4-{[(4*RS*,5*RS*)-3-(ethoxycarbonyl)-4,5-dihydro-5-phenyl-1*H*-pyrazol-4-yl]carbonyl}-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate 5-Oxide*; **10**): *Isomer a:* Yield 0.3 g (12%). M.p. 160–163°. IR (KBr): 1793, 1734, 1654, 1522. ^{1}H-NMR ($CDCl_3$): 0.76 (*t*, *J* = 7.1, $COOCH_2$*Me*); 2.05 (*s*, Me–C(3)); 3.57–3.80 (*m*, $COOCH_2$Me); 3.84 (*s*, COOMe); 4.63 (*d*, *J* = 13.4, H–C(4′)); 4.91 (*d*, *J* = 4.8, H–C(6)); 5.06 (*d*, *J* = 13.4, H–C(5)); 5.98 (*s*, H–C(2)); 6.24 (*dd*, *J* = 9.6, 4.8, H–C(7)); 7.01–7.10 (*m*, 2 arom. H); 7.13–7.52 (*m*, 6 arom. H, NHCO); 7.77–7.81 (*m*, 2 arom. H); 8.15 (*s*, H–N(1′)). ^{13}C-NMR ($CDCl_3$): 13.4 ($COOCH_2$*Me*); 19.1 (*Me*–C(3)); 50.2 (C(4′)); 52.6 (COO*Me*); 58.8 (C(7)); 61.7 ($COOCH_2$Me); 65.3 (C(6)); 66.1 (C(2)); 69.2 (C(5′)); 123.2 (C(3)); 123.7 (C(4)); 127.4, 127.9, 128.7 (2 arom. CH); 126.7, 128.2, 129.3, 132.2 (1 arom. CH); 132.6, 135.1 (2 arom. quat. C); 149.1 (C(3′)); 161.6, 163.3, 166.9, 167.7, 183.2 (5 CO). Anal. calc. for $C_{29}H_{28}N_4O_8S$ (592.63): C 58.78, H 4.76, N 9.45, S 5.41; found: C 58.62, H 4.77, N 9.21, S 5.76.

Isomer b: Yield 0.31 g (13%). ^{1}H-NMR ($CDCl_3$): 0.74 (*t*, *J* = 7.2, $COOCH_2$*Me*); 2.13 (*s*, Me–C(3)); 3.62 (*q*, $COOCH_2$Me); 3.87 (*s*, COOMe); 4.45 (*d*, *J* = 5.8, H–C(6)); 4.65 (*d*, *J* = 13.4, H–C(4′)); 5.05 (*d*, *J* = 13.5, H–C(5′)); 6.01 (*s*, H–C(2)); 6.16 (*dd*, *J* = 9.8, 5.8, H–C(7)); 6.97–7.90 (*m*, 9 arom. H, NHCO); 8.15 (*s*, H–N(1′)). ^{13}C-NMR ($CDCl_3$): 13.4 ($COOCH_2$*Me*); 19.3 (*Me*–C(3)); 50.0 (C(4′)); 52.6 (COO*Me*); 58.8 (C(7)); 61.7 ($COOCH_2$Me); 65.3 (C(6)); 66.8 (C(2)); 69.0 (C(5′)); 122.7 (C(3)); 123.8 (C(4)); 127.4, 127.9, 128.7, 128.8 (2 arom. CH); 128.3, 132.3 (1 arom. CH); 132.6, 135.0 (2 arom. quat. C); 148.7 (C(3′)); 161.6, 163.5, 166.7, 167.7, 182.7 (5 CO). Anal. calc. for $C_{29}H_{28}N_4O_8S$ (592.63): C 58.78, H 4.76, N 9.45, S 5.41; found: C 58.62, H 4.79, N 9.79, S 5.07.

Reactions of **1** *or* **3** *with Diazomethane.* A soln. of **1** (310 mg) or **3** (1.5 g) in CH_2Cl_2 (20 ml) (for **3**, 60 ml was used) was cooled to 0°, and the same volume of an Et_2O soln. of diazomethane was added. After 1 h, a few drops of AcOH were added, and the mixture was washed with identical volumes of 10% $NaHCO_3$ soln. and H_2O. The org. phase was dried ($MgSO_4$) and evaporated in a water-bath at 20°. The residual oil was purified by CC (toluene/AcOEt 5:1): **12** or **13**, resp.

*Methyl (2*E*,6*R*,7*R*)-7-Benzamido-3-*C*-deacetoxy-2-[(2*E*)-methoxybut-2-enylidene]cephalosporanate 1-Oxide* (= *Methyl (4*E*,6*R*,7*R*)-7-(Benzoylamino)-4-[(2*E*)-1-methoxybut-2-enylidene]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 5-Oxide*; **12**). Yield 21%. M.p. 220–223°. IR (KBr): 1783, 1721, 1527, 1447. ^{1}H-NMR ($CDCl_3$): 1.99 (*dd*, *J* = 1.5, 6.6, Me–C(1′)); 2.35 (*s*, Me–C(3)); 3.80 (*s*, MeO–C(2′)); 3.91 (*s*, COOMe); 4.49 (*d*, *J* = 4.5, H–C(6)); 6.17–6.27 (*m*, H–C(7), H–C(3′)); 6.42–6.56 (*m*, H–C(2′)); 7.42–7.55 (*m*, 4 arom. H); 7.82–7.87 (*m*, 1 arom. H, CONH). ^{13}C-NMR ($CDCl_3$): 17.3 (*Me*–C(3)); 18.9 (*Me*–C(4′)); 52.5 (C(6)); 58.8 (C(7)); 59.6 (*Me*O–C(1′)); 69.4 (COO*Me*); 114.7 (C(2)); 121.2 (C(4)); 121.7 (C(2′)); 127.4 (2 arom. CH); 128.7 (2 arom. CH); 129.7 (C(3)); 132.3 (arom. CH); 132.8 (arom. quat. C); 142.7 (C(3′)); 147.2 (C(2′)); 164.0, 165.4, 166.9 (3 CO). Anal. calc. for $C_{21}H_{22}N_2O_6S$ (430.48): C 58.59, H 5.15, N 6.51; found: C 58.71, H 5.29, N 6.53.

*Methyl (2*E*,6*R*,7*R*)-7-Benzamido-3-*C*-deacetoxy-2-[(2*E*)-1-methoxy-3-phenylallylidene]cephalosporanate 1-Oxide* (= *Methyl (4*E*,6*R*,7*R*)-7-(Benzoylamino)-4-[(2*E*)-1-methoxy-3-phenylprop-2-enylidene]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate 5-Oxide*; **13**). Yield 27%. Yellow oil. IR (KBr): 1792, 1718, 1654, 1507. ^{1}H-NMR ($CDCl_3$): 2.39 (*s*, Me–C(3)); 3.87 (*s*, MeO–C(1′)); 3.92 (*s*, COOMe); 4.60 (*d*, *J* = 4.6, H–C(6)); 6.23 (*dd*, *J* = 4.6, 9.9, H–C(7)); 7.02–7.29 (*m*, C*H*=C*H*–Ph); 7.36–7.55 (*m*, 7 arom. H); 7.81–7.96 (*m*, 3 arom. H, CONH). ^{13}C-NMR ($CDCl_3$): 17.3 (*Me*–C(3)); 52.6 (C(6)); 59.4 (C(7)); 60.0 (*Me*O–C(1′)); 69.8 (COO*Me*); 118.0 (C(2′)); 120.0 (C(4)); 120.3 (C(2)); 127.4 (2 arom. CH); 127.9 (2 arom. CH); 128.7 (2 arom. CH); 129.0 (2 arom. CH); 130.3 (arom. CH); 132.3 (arom. CH); 131.5, 134.5 (2 arom. quat. C); 141.4 (C(3′)); 205.3 (C(2′)); 162.3, 164.0, 164.6 (3 CO). Anal. calc. for $C_{26}H_{24}N_2O_6S$: C 63.40, H 4.91, N 5.69, S 6.51; found: C 63.71, H 5.31, N 6.20, S 6.56.

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Received February 18, 2002