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SYNTHESIS AND STRUCTURAL MODIFICATION OF *tert*-BUTYL ESTER OF 7α-CHLORO-2-(N,N-DIMETHYLAMINOMETHYLENE)-3-METHYL-1,1-DIOXOCEPH-3-EM-4-CARBOXYLIC ACID*

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The reaction of tert-butyl 7α-chloro- and 7-β-chloro-7α-isopropoxy-3-methyl-1,1-dioxoceph-3-em-4-carboxylates with the Vilsmeier reagent was carried out with introduction of N,N-dimethylaminomethylene group at position 2 in the E- and Z-isomeric forms. Prolonged treatment of tert-butyl 7α-chloro-3-methyl-2-(N,N-dimethylaminomethylene)-1,1-dioxoceph-3-em-4-carboxylate with hydroxylamine hydrochloride in acetonitrile at 40-50°C gave tert-butyl 10(S)-chloro-6-methyl-5-oxa-1,1,9-trioxo-1-thia-4,8-diazatricyclo[7,2,0,0^{2,6}]undecane-7(R)-carboxylate which isomerized into 1-tert-butoxycarbonylmethyl-3α-chloro-4-(5-methylisoxazole-4-sulfonyl)azetidin-2-one. In the case of tert-butyl 7β-chloro-7α-isopropoxy-3-methyl-2-(N,N-dimethylaminomethylen)-1,1-dioxoceph-3-em-4-carboxylate the analogous reaction gave tert-butyl 10β-chloro-(2S,6S,7S,10R,11R)-10α-isopropoxy-6-methyl-5-oxa-1,1,9-trioxo-1-thia-4,8-diazatricyclo[7,2,0,0^{2,6}]undecane-7(R)-carboxylate, the struc-ture of which was determined by 2D-NOESY two-dimensional spectroscopy. The compounds synthesized showed weak or no cytotoxic activity with respect to monolayers of cancer cells in vitro.

Keywords: *tert*-butyl 7β-chloro-7α-isopropoxy-3-methyl-2-(N,N-dimethylaminomethylene)-1,1-dioxoceph-3-em-4-carboxylate, *tert*-butyl 7β-chloro-7α-isopropoxy-3-methyl-1,1-dioxoceph-3-em-4-carboxylate, *tert*-butyl 10β-chloro-(2*S*,6S,7*S*,10*R*,11*R*)-10α-isopropoxy-6-methyl-5-oxa-1,1,9-trioxo-1-thia-4,8-diazatricyclo-[7,2,0,0^{2,6}]undecane-7(*R*)-carboxylate, *tert*-butyl 7α-chloro-3-methyl-1,1-dioxoceph-3-em-4-carboxylate, *tert*-butyl 7α-chloro-3-methyl-2-(N,N-dimethylaminomethylene)-1,1-dioxoceph-3-em-4-carboxylate, 1-*tert*-butoxycarbonylmethyl-3α-chloro-4-(5-methylisoxazole-4-sulfonyl)azetidin-2-one.

We have shown previously that the cephem heterocyclic system **1a** oxidized to sulfone in position 1, and also substituted at positions 3, 4, and 7α, respectively with a methyl, an ester group and a chlorine have potential as pharmacophore of anticancer activity [1].

In a continuation of the investigation of the relation between the structure and the anticancer properties of structural analogs of cephalosporin we have carried out structural modifications of system **1a** based on the introduction of N,N-dimethylaminomethylene group at position 2 and subsequent chemical conversion of the

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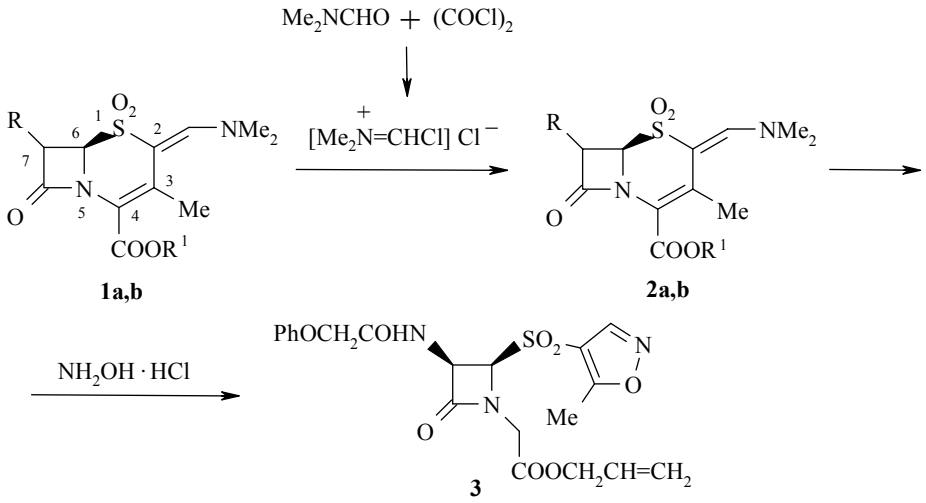
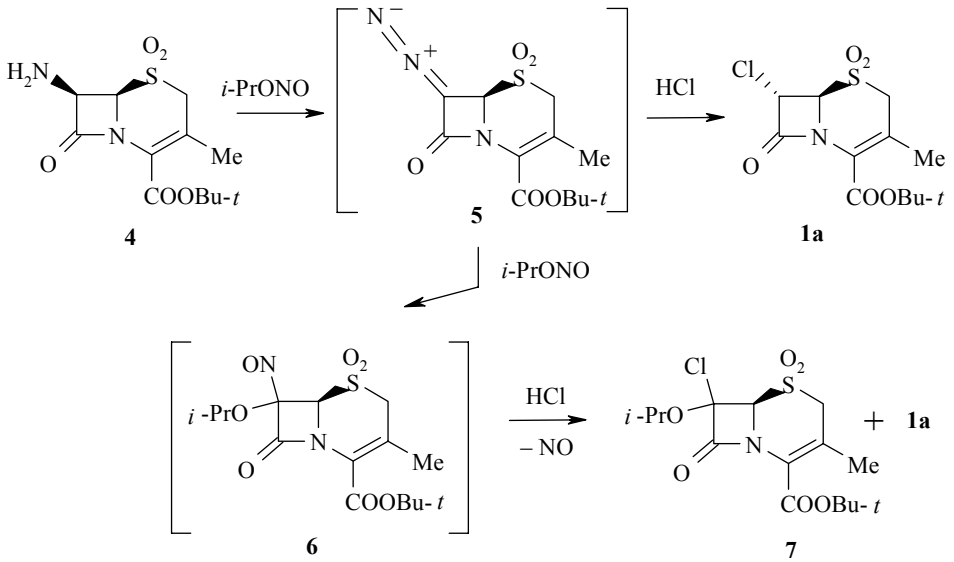
corresponding compound **2a**. We were guided by paper [2] on the preparation of allyl 3-methyl-2-(N,N-dimethylaminomethylene)-1,1-dioxo-7β-phenoxymethylcarbonylaminoceph-3-em-4-carboxylate (**2b**) and its interaction with hydroxylamine to give the azetidin-2-one **3** with the 5-methyl-4-isoxazolesulfonyl group in position 4.



1,2 a R = (*S*)Cl, R^1 = *t*-Bu; **b** R = (*R*)$PhOCH_2CONH$, R^1 = $CH_2CH{=}CH_2$

This reaction drew our attention by the original method for the preparation of 4-hetarylsulfonyl-substituted β-lactams, some examples of which have high cytotoxicity *in vitro* with respect to cancer cells [3].

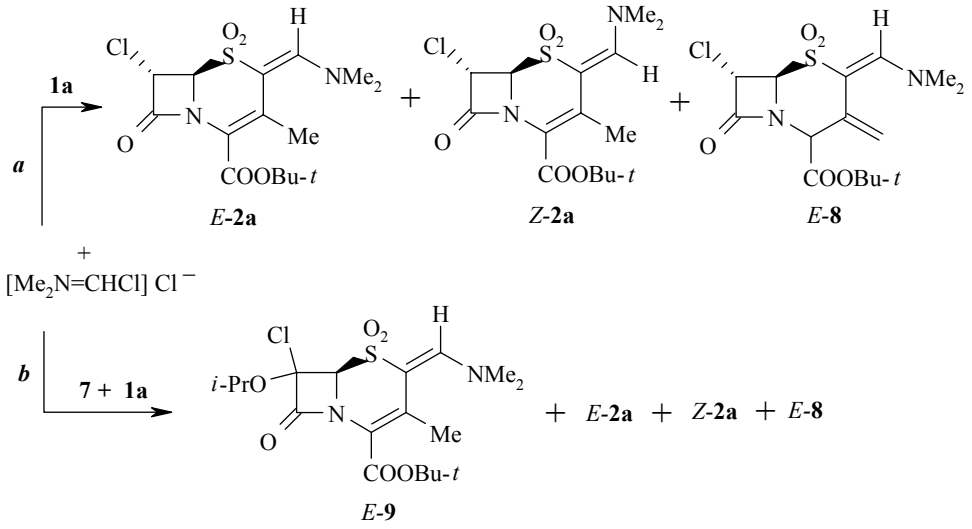
The *tert*-butyl 7α-chloro-3-methyl-1,1-dioxoceph-3-em-4-carboxylate starting material (**1a**) was synthesized according to a method [4] by diazotization of 7β-amino-3-methyl-1,1-dioxoceph-3-em-4-carboxylic acid (**4**) with isopropyl nitrite, with subsequent removal of the excess of this reagent at low pressure, and displacement of the diazo group in the intermediate compound by a chlorine atom using hydrogen chloride. Exclusion of the removal of excess isopropyl nitrite by evaporation led to the a chromatographically inseparable mixture of the 7α-chloro-substituted cephem **1a** and a new substance **7** in a 1:1 ratio. Their ^{1}H NMR spectra



were characterized by coincidence of the signals of the protons on C-2 and the substituents at positions 3, 4, and 6. The principal difference in the spectrum of compound **7** is the presence of the signals of two methyl and one methyne group, which indicates unambiguously the presence of an isopropyl group in position 7. The mechanism of such reaction assumes the partial substitution of the diazo group in compound **5** by the excess isopropyl nitrite to give the 7-isopropoxy-7-nitroso-disubstituted intermediate compound **6** with subsequent displacement of the NO group by a chlorine atom.

The introduction of the N,N-dimethylaminomethylene group at position 2 of the cephem nucleus of compound **1a** was carried out by a method cited elsewhere [1, 2] using the Vilsmeier reagent (scheme 1, reaction ***a***). The reaction was carried out at 0°C in acetonitrile for 1.5 h, after which a base was added to the reaction mixture. The nature of the base affected the yield of the reaction: DBU gave 12%, triethylamine 58% and pyridine 63% yield of isomeric products, consisting of a chromatographically inseparable mixture of 2(*E*)-and 2(*Z*)-N,N-dimethylaminomethylene-substituted cephems *E*-**2a** and *Z*-**2a** in a ratio of 3 : 1, and cepham *E*-**8,** formed by shift of the double bond in compound *E*-**2a**.

Scheme 1



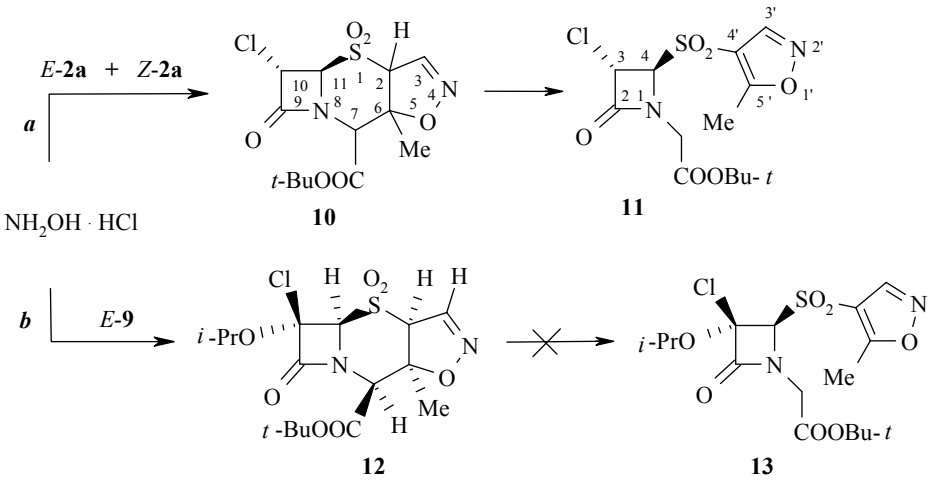
The structures of isomers *E*-**2a** and *Z*-**2a** were determined by 2D-NOESY two-dimensional spectroscopy [1]. Comparative analysis of their spectroscopic data showed that the closeness of the sulfonyl and dimethylamino groups in isomer *Z*-**2a** led to a weak field shift of the protons of the $N(CH_3)_2$ group (3.35 ppm) in comparison with those of the *E*-**2a** isomer (3.01 ppm). For the same reason, the presence in the ^1H NMR spectrum of compound **8** of the signals of the protons of the dimethylaminomethylene group in the 2.96 ppm region indicates that the N,N-dimethylaminomethylene group is in the *E*-isomeric form.

To judge from TLC, treatment of a mixture of 7-mono- and 7-disubstituted cephems **1a** and **7** with the Vilsmeier reagent under analogous conditions led to several products (scheme 1, reaction ***b***). Fractionation by column chromatography permitted the isolation in pure form of the 7-chloro-2(*E*)-(N,N-dimethyl-aminomethylene)-7-isopropoxy-substituted cephem *E*-**9** and its characterization by ^1H and ^{13}C NMR and mass spectra.

In a continuation of this investigation, cephem **2a**, as a mixture of *E*- and *Z*-isomers, was treated with hydroxylamine hydrochloride in acetonitrile at 40-50°C for 6 days (scheme 2, reaction ***a***). With the help of column chromatography the end product **11** was isolated from the reaction mixture and characterized by ^1H NMR and mass spectra. Its mixture with the tricyclic lactam **10** was also characterized.

The results obtained are in excellent agreement with a mechanism cited in [2] for conversion of cephem **2** into the azetidinone **3**, despite the difference in the nature and configuration of the substituents in position 7.

Scheme 2



Treatment of 7-chloro-2(*Z*)-(N,N-dimethylaminomethylene)-7-isopropoxy-substituted cephem **9**-*E* with hydroxylamine hydrochloride under analogous conditions gave only the tricyclic product **12** (scheme 2, reaction ***b***). Attempts to isomerize it into the azetidinone-2 **13** at higher temperature in acetonitrile or by UV-irradiation were unsuccessful. The two-dimensional 2D-NOESY spectroscopy was used to analyse the special disposition of the substituents in the tricyclo[7,2,0,$0^{2,6}$]undecanoic system **12** revealed NOE between protons in positions 2, 7, and 11, and also between the protons of the methyl and isopropyl groups in positions 6 and 10. This, together with the known *R*-configuration at atom C-11, allows the unambiguous establishment of the four chiral centers: 2*S*, 6*S*, 7*S*, and 10*R*. The information obtained in this way confirms that in the previously synthesized precursors of this compound: **7** and *E*-**9**, the isopropoxy group is in the α-position, and the chlorine atom in the β-position, relative to the plane of the β-lactam ring.

The biological screening of the synthesized compounds *in vitro* included their cytotoxic properties in relation to monolayers of lines of cancer cells HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) in comparison with toxicity with respect to normal 3T3 cells (mouse embryonic fibroblasts). Fibroblasts 3T3 dyed with neutral red, not subjected to experiment *in vivo*, permitted calculation of the expected LD_{50} toxicity for the compounds tested, using a special equation [5].

The results cited in Table 1 indicate that the cephems *E*-**2a**/*Z*-**2a** and cepham *E*-**8**, formed by the introduction of the N,N-dimethylaminomethylene group into position 2 of *tert*-butyl esters of 7-chloro-3-methyl-1,1-dioxo-ceph-3-em-4-carboxylic acids, are characterized by low cytotoxicity with respect to cancer cells, and also a low LD_{50} index in comparison with that of the initial cephem **1a**. Analogous tendencies were observed for the monocyclic β-lactam **11** with a 5-methyl-4-sulfonylisoxazole system in position 4, and also for its mixture with the tricyclic lactam, **10/11** (1:1).

Introduction of an isopropoxy group in addition to a chlorine atom in position 7 of the bicyclic and tricyclic β-lactam-containing compounds *E*-**9** and **12** led to practically nontoxic compounds which at concentrations of 200 μg/ml stimulated the growth of both cancer and normal cells, and which are consequently characterized by very high values of the expected toxicity with LD_{50} > 2300 mg/kg.

Table 1. Biological Properties of Structural Analogs of *tert*-Butyl 7-Chloro-3-methyl-1,1-dioxoceph-3-em-4-carboxylate

Compound	Cytotoxic activity *in vitro*, LC_{50}, μγ/ml*					LD_{50}, mg/kg
	HT-1080		MG-22A		3T3	
	CV	MTT	CV	MTT	NR	
1a	6	6	6	2	226	1162 [1]
E-**2a**/*Z*-**2a** (3:1)	18	32	18	21	96	878
E-**8**	52	100	29	45	220	1244
E-**9**	*[2]	*[2]	*[2]	*[2]	803	2355
11	100	>100	36	32	501	1751
10/11 (1:1)	30	33	23	24	107	912
12	*[2]	*[2]	*[2]	*[2]	740	2305

* LC_{20} – concentration required for 50% cell destruction; CV – crystal violet; MTT – 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide; NR – neutral red.
*[2] Stimulated the growth of the cell population.

EXPERIMENTAL

^1H and ^{13}C NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded on Varian Mercury-200 (200 MHz for ^1H) and Varian Mercury-400 (400 and 100 MHz respectively) instruments. Elemental analyses were carried with a Carlo Erba 1108 analyzer. ESI-MS (mass spectrometer with inductively coupled plasma) were recorded with a Micromass Quatro micro™ API instrument. Reactions were monitored by TLC on Merck Kieselgel plates with development by UV light. Merck Kieselgel (0.063-0.230 mm) was used for preparative column chromatography. Acros and Aldrich reagents and materials were used in the experiments.

A 4096 x 1024 matrix was used for recording 2D-spectra, with the provision for ^1H τ_{2max} = 250 msec for registration on the *F*2 axis and τ_{1max} = 100 msec for the *F*1 axis. To improve the signal-noise ratio the matrix was subjected to Fourier transformation with addition of two zeros and expansion of the cosine function. The mixing time in the 2D-NOESY was 1 sec.

The optical density in the biological tests carried out on a 96-hole plate, was determined with a Tetrtek Multiscan MCC/340 horizontal spectrophotometer.

Mixture of *tert*-Butyl 7α-Chloro-3-methyl-1,1-dioxoceph-3-em-4-carboxylate (1a) and *tert*-Butyl 7β-Chloro-7-α-isopropoxy-3-methyl-1,1-dioxoceph-3-em-4-carboxylate (7) (1:1). Isopropyl nitrite (1.7 g, 20 mmol) and trifluoroacetic acid (16 μl) were added to a solution of *tert*-butyl 7-amino-3-methyl-1,1-dioxo-ceph-3-em-4-carboxylate (3.8 g, 13 mmol) in dichloromethane (250 ml) at 5°C. The mixture was stirred for 1.5 h at room temperature and then ethyl acetate (3.4 ml, saturated with dry HCl) was added. The reaction mixture was stirred for 2.5 h at 5°C and then washed with a saturated aqueous solution of NH_4Cl until a pH ~ 7 was achieved. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was fractionated by column chromatography on silica gel with ethyl acetate–hexane as eluent, changing from 1:5 to 1:1. The fraction with R_f 0.55 (ethyl acetate–hexane, 1:2) was collected and evaporated to give a mixture of **1a** and **7** (2.3 g, 54%). ^1H NMR spectrum, δ, ppm (*J*, Hz): **1a** – 1.54 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 3.66 and 3.89 (2H, two d, AB system, ^2J = 18.4, SO_2CH_2); 4.71 (1H, d, ^3J = 1.5, H-6); 5.25 (1H, d, ^3J = 1.5, H-7). **7** – 1.28 and 1.31 (6H, two d, ^3J = 6.4, 2 CH_3 *i*-Pr). 1.54 (9H, s, C_4H_9), 2.14 (3H, s, CH_3); 3.61 and 3.79 (2H, two d, AB system, ^2J = 17.5, SO_2CH_2); 4.48-4.65 (1H, sept,

^3J = 6.4, CH *i*-Pr); 4.71 (1H, s, H-6). ^{13}C NMR, δ, ppm: **1a** – 19.23 (CH_3); 27.80 ($C(\underline{C}H_3)_3$); 55.27 (C-7); 55.62 (C-2); 71.35 (C-6); 84.27 ($\underline{C}Me_3$); 124.27 (C-4); 127.16 (C-3); 157.3 (C-8); 159.27 (COO).

Mixture of *tert*-Butyl 7α-Chloro-2(*E*)-2-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxoceph-3-em-4-carboxylate (*E*-2a) and *tert*-Butyl 7α-Chloro-2(*Z*)-2-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxoceph-3-em-4-carboxylate (*Z*-2a) (3:1). A mixture of oxalyl chloride (2.16 ml, 24.86 mmol) and DMF (1.93 ml, 24.86 mmol) in acetonitrile (25 ml) was added to a stirred suspension of the sulfone of *tert*-butyl 7α-chloro-3-methyl-1,1-dioxoceph-3-em-4-carboxylate (2.00 g, 6.22 mmol) in acetonitrile (25 ml) at -5°C under argon. The reaction mixture was stirred for 1.5 h at 0°C, neutralized with dry pyridine (2.01 ml, 24.86 mmol), diluted with 5% aqueous NaCl (100 ml) and extracted with ethyl acetate (2×30 ml). The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated at low pressure. The residue was fractionated by column chromatography on silica gel with ethyl acetate-hexane as eluent, varying from 1:10 to 1:2. The fraction with R_f 0.44 (ethyl acetate–hexane, 1:1) was collected and evaporated to give a mixture of *E*-**2a** and *Z*-**2a** (0.85 g, 38%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *E*-**2a** – 1.53 (9H, s, C_4H_9); 2.21 (3H, s, 3-CH_3); 3.01 (6H, s, $N(CH_3)_2$); 4.77 (1H, d, ^3J = 1.5, H-6); 5.06 (1H, d, ^3J = 1.5, H-7); 7.29 (1H, s, =$CHNMe_2$). *Z*-**2a** – 1.53 (9H, s, C_4H_9); 2.22 (3H, s, 3-CH_3); 3.35 (6H, s, $N(CH_3)_2$); 4.55 (1H, d, ^3J = 1.5, H-6); 5.24 (1H, d, ^3J = 1.5, H-7); 7.02 (1H, s, =$CHNMe_2$). ^{13}C NMR spectrum, δ, ppm: *E*-**2a** – 21.70 (CH_3); 28.02 ($C(\underline{C}H_3)_3$); 43.52 ($N(\underline{C}H_3)_2$); 56.71 (C-7); 73.35 (C-6); 83.06 ($\underline{C}Me_3$); 99.57 (C-2); 123.44 (C-4); 134.67 (C-3); 148.78 ($\underline{C}H$-NMe_2); 160.39 (C-8); 160.70 (COO); *Z*-**2a** – 21.70 (CH_3); 27.91 ($C(\underline{C}H_3)_3$); 48.83 ($N(\underline{C}H_3)_2$); 56.17 (C-7); 71.06 (C-6); 82.59 ($\underline{C}Me_3$); 101.58 (C-2); 123.44 (C-4); 134.67 (C-3); 149.82 ($\underline{C}H$-NMe_2); 160.39 (C-8); 160.70 ($\underline{C}OO$). Found, %: C 47.91; H 5.67; N 7.07. $C_{15}H_{21}ClN_2O_5S$. Calculated, %: C 47.81; H 5.62; N 7.43.

***tert*-Butyl 7α-Chloro-2(*E*)-2-(N,N-dimethylaminomethylene)-3-methylene-1,1-dioxocepham-4-carboxylate (*E*-8)** was isolated during fractionation of the reaction mixture, described in the previous experiment, from the fraction with R_f 0.41 (ethyl acetate–hexane, 1:1) as yellow crystals (0.56 g, 25%), mp 43-46°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, C_4H_9); 2.96 (6H, s, $N(CH_3)_2$); 4.75 (1H, d, ^3J = 1.2, H-6); 4.92 (1H, s, H-4); 5.14 (1H, d, ^3J = 1.2, H-7); 5.33 (1H, s, =CH_2); 5.66 (1H, s, =CH_2); 7.12 (1H, s, =$C\underline{H}NMe_2$). ESI-MS (MeCN): 377 [MH^+].

***tert*-Butyl 7β-Chloro-2(*E*)-7α-isopropoxy-3-methyl-2-(N,N-dimethylaminomethylene)-1,1-dioxoceph-3-em-4-carboxylate (*E*-9)** was obtained from the reaction of the Vilsmeier reagent on a mixture of **1a** and **7** (1:1), analogous to method used for **1a**, from the fraction with R_f 0.60 (ethyl acetate–hexane 1:1), as yellow crystals, yield 66%, mp 59-63°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (6H, d, ^3J = 6.5, 2 CH_3 *i*-Pr); 1.51 (9H, s, C_4H_9); 2.31 (3H, s, CH_3); 3.04 (6H, s, $N(CH_3)_2$); 4.41-4.63 (1H, sept, ^3J = 6.5, CH *i*-Pr); 4.84 (1H, s, H-6); 7.19 (1H, s, =$C\underline{H}NMe_2$). ^{13}C NMR spectrum, δ, ppm: 22.66 ($\underline{C}H_3$); 22.91 ($CH(\underline{C}H_3)_2$); 28.04 ($C(\underline{C}H_3)_3$); 43.13 (NMe_2); 73.04 ($\underline{C}HMe_2$); 79.98 (C-6); 82.65 ($\underline{C}Me_3$); 100.61 (C-2); 101.30 (C-7); 122.55 (C-4); 141.8 (C-3); 148.80 ($\underline{C}HNMe_2$); 160.66 (C-8); 160.67 (COO). ESI-MS (MeCN): 435 [MH^+].

1-*tert*-Butoxycarbonylmethyl-3α-chloro-4-(5-methylisoxazole-4-sulfonyl)azetidin-2-one (11). A solution consisting of acetonitrile (75 ml), *tert*-butyl 7α-chloro-3-methyl-2-(N,N-dimethylaminomethylene)-1,1-dioxoceph-3-em-4-carboxylate (600 mg, 1.59 mmol), and hydroxylamine hydrochloride (221 mg, 3.18 mmol) was stirred for 144 h at 40-50°C. The reaction mixture was evaporated at low pressure. The residue was fractionated by column chromatography on silica gel with ethyl acetate-hexane, changing from 1:5 to 1:2. The fraction with R_f 0.60 (ethyl acetate–hexane, 1:2) was collected and evaporated to give white crystals (81 mg, 14%), mp 119-120°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, C_4H_9); 2.76 (3H, s, CH_3); 3.79 and 4.38 (2H, two d, ^2J = 18.5, $NC\underline{H}_2COO$); 4.92, (1H, d, ^3J = 1.8, H-4); 5.15 (1H, d, ^3J = 1.8, H-3); 8.46 (1H, s, H-3', isoxazole). ^{13}C NMR spectrum, δ, ppm: 12.13 (CH_3); 27.39 ($C(\underline{C}H_3)_3$); 43.54 ($N\underline{C}H_2$); 57.77 (C-4); 77.32 (C-3); 84.22 ($\underline{C}Me_3$); 113.61 (C-5'); 148.71 (C-3'); 161.30 (C-2); 165.77 (C=O); 175.46 (C-4'). ESI-MS (MeCN): 387 [MNa^+].

Mixture of 1-*tert*-Butoxycarbonylmethyl-3α-chloro-4-(5-methylisoxazole-4-sulfonyl)azetidin-2-one (11) and *tert*-Butyl 10(*S*)-Chloro-6-methyl-5-oxa-1,1,9-trioxo-1-thia-4,8-diazatricyclo[7,2,0,$0^{2,6}$]undecane-7(*R*)-carboxylate (10). Compound **10** was isolated during fractionation of the reaction mixture, described in the

previous experiment, from the fraction with R_f 0.34 (ethyl acetate–hexane: 1:2), with a yield of 272 mg (47%). ^{1}H NMR spectrum (after removal of the signals belonging to isomer **11),** δ, ppm (*J*, Hz): 1.34 (3H, s, CH_3); 1.56 (9H, s, C_4H_9); 4.45 (1H, d, ^3J = 1.9, H-2); 4.78 (1H, m, H-7); 5.05 (1H, d, ^3J = 1.4, H-11); 5.25 (1H, d, ^3J = 1.4, H-10); 7.51 (1H, d, ^3J = 1.9, H-3). ^{13}C NMR spectrum, δ, ppm: 22.80 (CH_3); 27.85 (C($\underline{C}H_3)_3$); 54.22 (C-7); 58.53 (C-10); 72.94 (C-11); 75.93 (C-2); 86.38 ($\underline{C}Me_3$); 90.10 (C-6); 141.81 (C-3); 159.33 (C-9).

***tert*-Butyl 10β-Chloro-(2*S*,6*S*,7*S*,10*R*,11*R*)-10α-isopropoxy-6-methyl-5-oxa-1,1,9-trioxo-1-thia-4,8-diaza-tricyclo[7,2,0,0^{2,6}]undecane-7(*R*)-carboxylate (12)** was obtained by the reaction of hydroxylamine hydrochloride on compound *E*-**9** analogously to the method described for compound **11** from the fraction with R_f 0.60 (ethyl acetate–hexane, 1:1) as white crystals in a yield of 20 mg (20%), mp 131-133°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (6H, d, ^3J = 6.1, 2 CH_3 *i*-Pr); 1.48 (9H, s, C_4H_9); 1.56 (3H, s, CH_3)< 4.36 (1H, br. s, H-2); 4.51 (1H, sept, ^3J = 6.1, CH *i*-Pr); 4.71 (1H, s, H-7); 4.96 (1H, s, H-11); 7.53 (1H, br. s, H-3). ^{13}C NMR spectrum, δ, ppm: 22.71 (CH($\underline{C}H_3)_2$); 24.99 (C($\underline{C}H_3)_3$); 27.85 (CH_3); 55.56 (C-7); 71.19 (C-11); 73.92 ($\underline{C}HMe_2$); 76.93 (C-2); 85.43 ($\underline{C}Me_3$); 89.25 (C-6); 101.18 (C-10); 139.8 (C-3); 160.38 (C-9); 163.27 (COO). ESI-MS (MeCN): 445 [MNa^+].

Biological Screening. The cytotoxic properties *in vitro* of the compounds synthesized relative to monolayers of HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma) cancer cells and 3T3 normal cells (mouse embryo fibroblasts) were determined with 96 hole plates using CV, MTT, and NR dyes according to methods [6, 7] , tested previously by us [4].

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