Chemistry of Heterocyclic Compounds, Vol. 45, No. 2, 2009

SYNTHESIS AND CYTOTOXIC ACTIVITY OF DERIVATIVES OF THE *tert*-BUTYL ESTER OF 7*Z*-ACETYLMETHYLENE-3-METHYL-3-CEPHEM-4-CARBOXYLIC ACID

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The condensation of the acetylmethylene group in the tert-butyl esters of 7Z-acetylmethylene-3-methyl-3-cephem-4-carboxylic acid and 7Z-acetylmethylene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid and in 7Z-acetylmethylene-3-methylene-1,1-dioxo-3-cephem with arylmethoxyamines and O-alkylation of the tert-butyl ester of 7Z-(2-hydroxyimino)propylidene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid using substituted benzyl bromides as well as pyridylmethyl chlorides gave arylmethoxyimino and pyridylmethoxyimino derivatives of these compounds in the syn and anti isomeric forms. The Vilsmaier reagent was used to introduce the N,N-dimethylaminomethylene group at C-2 of the cephem system in the tert-butyl esters of 7Z-[2-(arylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid. Subsequent transformation of the N,N-dimethylaminomethylene cephems using hydroxylamine led to 3Z-[2-(anti-arylmethoxyimino)propylidene]-tert-butoxycarbonylmethyl-4-(5-methyl-4-isoxazolylsulfonyl)-azetidin-2-ones. Condensation of the acetyl group in the tert-butyl ester of 7Z-acetylmethylene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid with 4-bromophenylhydrazine gave a cephem with a 2-(4-bromophenylhydrazono)propylidene group at C-7. Acylation of the tert-butyl ester of 7Z-(2-hydroxyimino)propylidene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid by 2-bromobenzoyl chloride gave a cephem with a 2-(2-bromo-benzoyloxyimino)propylidene group at C-7. Biological screening of these products towards to malignant and normal cells in vitro showed that their antitumor activity and cytotoxic selectivity towards to malignant and normal cells depend on the structure and configuration of the arylmethoxyimino and pyridylmethoxyimino groups in the 7-alkylidene substituent as well as on the presence or absence of N,N-dimethylaminomethylene and carboxyl groups, respectively, at C-2 and C-4 of the cephem system.

Keywords: 3*Z*-[2-(arylmethoxyimino)propylidene]-1-*tert*-butoxycarbonylmethyl-4-(5-methyl-4-isoxazolyl-sulfonyl)azetidin-2-ones, *tert*-butyl ester of 7*Z*-[2-(arylmethoxyimino)propylidene]-3-methyl-3-cephem-4-carboxylic acid, *tert*-butyl ester of 7*Z*-[2-(2-bromobenzoyloxyimino)propylidene]-3-methyl-1,1-dioxo-

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 284-303, February, 2009. Original article submitted November 12, 2008.

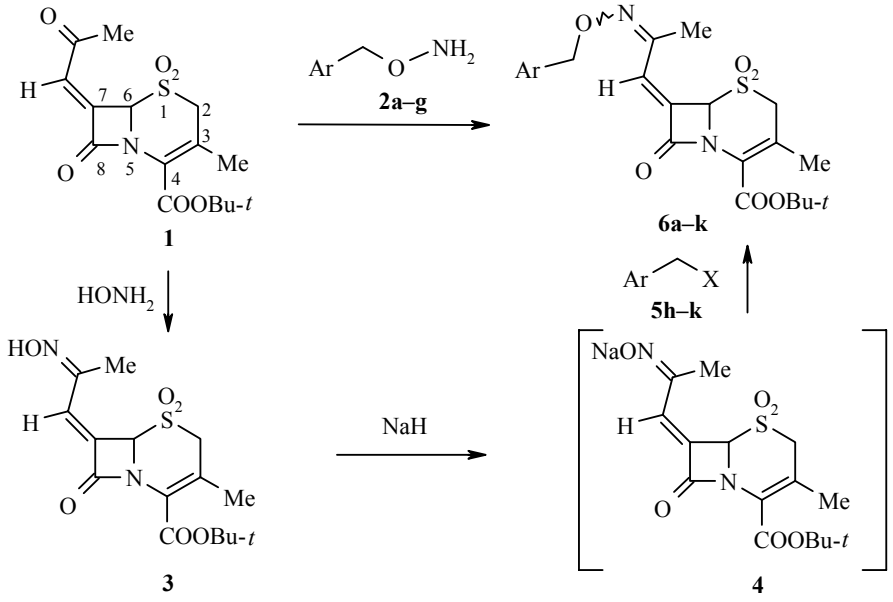
3-cephem-4-carboxylic acid, *tert*-butyl ester of 7*Z*-[2-(4-bromophenylhydrazono)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid, *tert*-butyl ester of 7*Z*-[2-(hydroxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid, *tert*-butyl esters of 7*Z*-[2-(arylmethoxyimino)-propylidene]-2-(dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid, *tert*-butyl esters of 7*Z*-(arylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid, *tert*-butyl esters of 3-methyl-1,1-dioxo-7*Z*-[2-(pyridylmethoxyimino)propylidene]-3-cephem-4-carboxylic acid.

In a continuation of a study of the relation between the structure and antitumor properties of cephalosporin derivatives, we have modified the cephem system and substituents in the previously synthesized *tert*-butyl ester of 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (**1**) [1].

The transformation of compound **1** and its arylmethoxyimino and pyridylmethoxyimino derivatives **6a-k** was carried out by two methods:

A. Condensation of the arylmethylene group with the hydrochloride salts of arylmethoxyamines **2a-g** in methanol in the presence of sodium acetate.

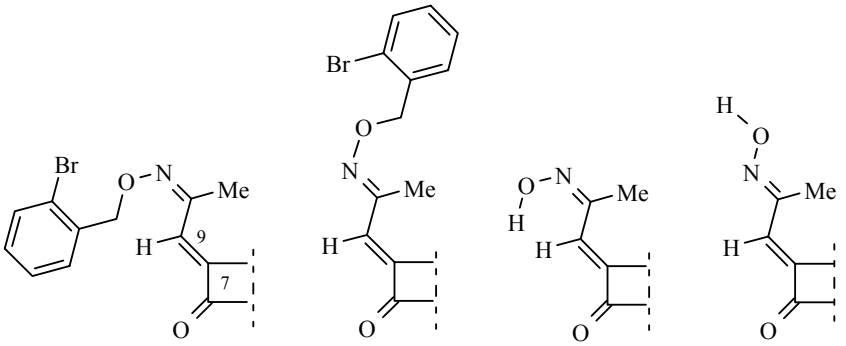
B. Oximination of the acetyl group in ester **1** with subsequent replacement of the hydrogen atom in the hydroxyimino group of the *tert*-butyl ester of 7*Z*-(2-(hydroxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (**3**) by sodium and O-aralkylation of the intermediate 3-cephem **4** by substituted benzyl bromides **5h**,**i** as well as 3- and 4-pyridylmethyl chlorides **5j**,**k**.



2, 6 a Ar = Ph, **b** Ar = 2-BrC_6H_4, **c** Ar = 3-BrC_6H_4, **d** Ar = 4-BrC_6H_4, **e** Ar = 2-ClC_6H_4, **f** Ar = 2-FC_6H_4, **g** Ar = 2-$CF_3C_6H_4$; **5, 6 h** Ar = 2,6-$Cl_2C_6H_3$, **i** Ar = 3,4-$Cl_2C_6H_3$, **j** Ar = 3-Py, **k** Ar = 4-Py; **5 h,i** X = Br, **j,k** X = Cl

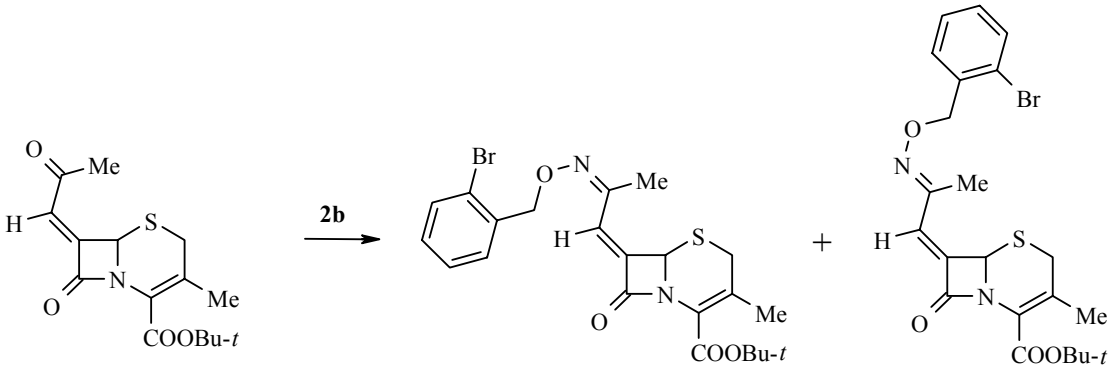
The cephalosporin derivatives **6a-k** synthesized by the two methods are formed as mixtures of *syn* and *anti* isomers. Esters **6a,b,e,f,g** were separated by column chromatography into pure isomers. The structural assignment of the *syn* and *anti* isomers was carried out using ^{1}H NMR 2D-NOESY spectroscopy for cephems **6b** and **3**.

The spectra of the *syn* isomers of both these compounds show cross peaks between the protons of the 9-CH and CH_2OH groups in cephem **6b** and, correspondingly, between the protons of the 9-CH and HON groups in cephem **3**. This effect is accompanied by a downfield shift of the signal for 9-CH in comparison with the analogous signal in *anti*-**6b** and *anti*-**3**, for which an Overhauser effect is not observed.



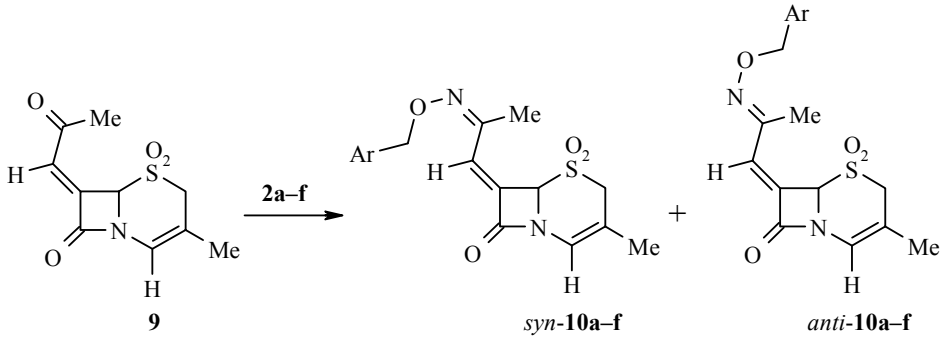
syn-**6b** *anti*-**6b** *syn*-**3** *anti*-**3**

To establish the biological activity on the oxidation degree of heterocyclic sulfur atom from *tert*-butyl ester of 7*Z*-acetylmethylene-3-methyl-3-cephem-4-carboxylic acid (**7**) [1], according to method A, its individual 2-brombenzyloxyimino derivatives of *syn*-**8b** and *anti*-**8b** were obtained.



7 *syn*-**8b** *anti*-**8b**

The condensation of previously synthesized 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem (**9**) [2] with arylmethoxyamines **2a-f** was carried out according to method A to evaluate the effect of esterification of the carboxyl group on the antitumor properties of cephems. The resultant mixtures of the *anti* and *syn* isomers of decarboxylated cephems **10a-f** were separated by column chromatography. The ^{1}H NMR spectra of cephems **10a-f** show a signal for H-4 at 6.56 ppm in accord with their structure.

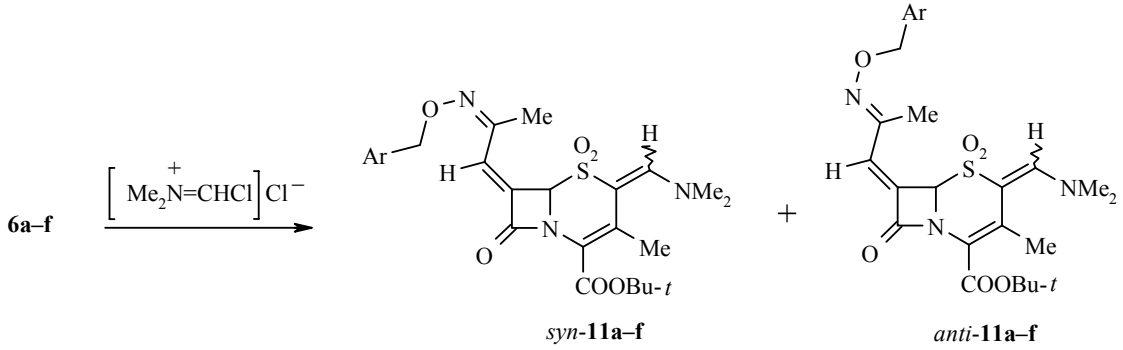


9 *syn*-**10a–f** *anti*-**10a–f**

2, 10 a Ar = Ph, **b** Ar = 2-BrC_6H_4, **c** Ar = 3-BrC_6H_4, **d** Ar = 4-BrC_6H_4,
e Ar = 2-ClC_6H_4, **f** Ar = 2-FC_6H_4

The introduction of an N,N-dimethylaminomethylene group at C-2 in the cephem system of the mixtures of the *syn* and *anti* isomers of **6a-f** using the Vilsmaier reagent was carried out according to our previous procedure [3].

Fractionation of the reaction products by column chromatography gave the *syn*-**11a-f** and *anti*-**11a-f** isomers as pure compounds. The presence of a double bond in this substituent provides the preconditions for finding the N,N-dimethylaminomethylene group in the *Z*- and *E*-isomeric forms.

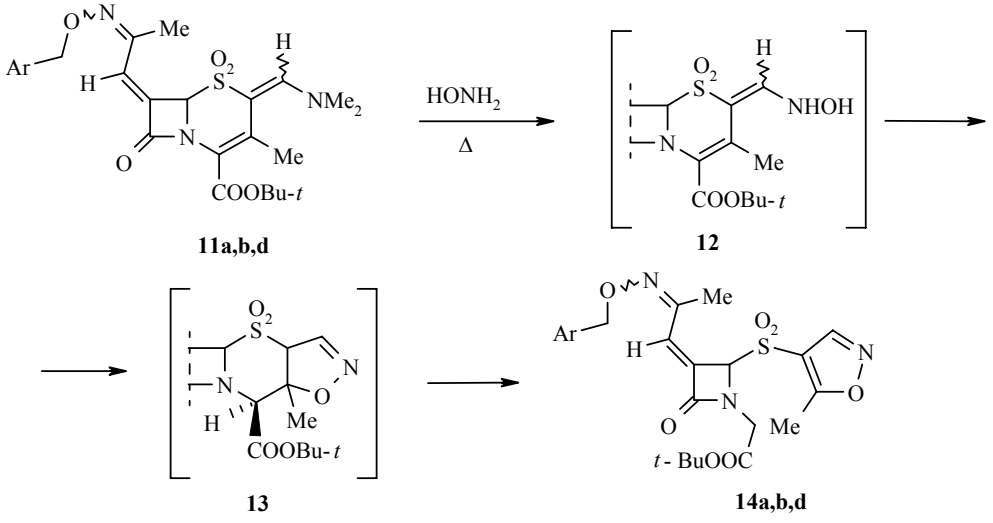


6, 11 a Ar = Ph, **b** Ar = 2-BrC_6H_4, **c** Ar = 3-BrC_6H_4, **d** Ar = 4-BrC_6H_4, **e** Ar = 2-ClC_6H_4, **f** Ar = 2-FC_6H_4

In accord with the spectral data for this type of compounds by ^{1}H NMR 2D-NOESY spectroscopy [3], we found the close proximity of the sulfone and dimethylamino groups in isomer 2*Z*-**11a-f** leads to a characteristic downfield shift of the signals of the NMe_2 protons in comparison with the analogous signals for the 2*E*-**11a-f** isomers.

2*Z*-**11a–f** 2*E*-**11a–f**

The action of hydroxylamine hydrochloride on a mixture of the *syn* and *anti* isomers of N,N-dimethylaminomethylenecephems **11a,b-d** in acetonitrile at 40-50°C for 2 h led to opening of the double bond in the 3-cephem system and formation of 2-azetidinones **14a,b**,**d** substituted at C-4

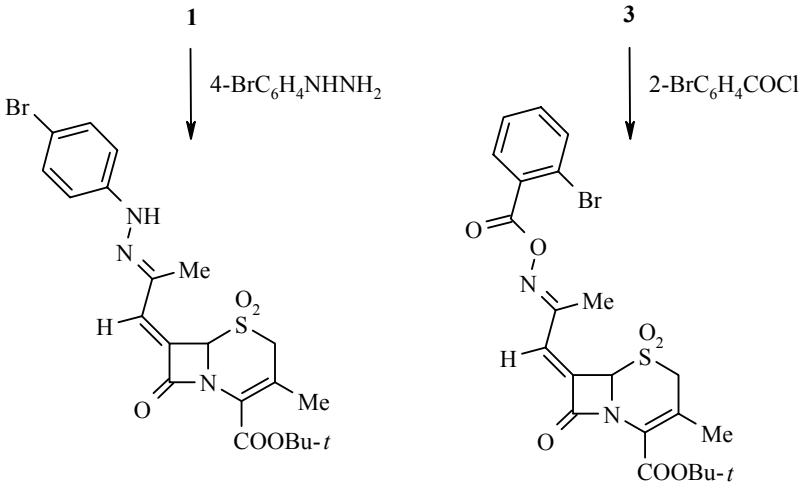


11, 14 a Ar = Ph, **b** Ar = 2-BrC_6H_4, **d** Ar = 4-BrC_6H_4,

of the 5-methylisoxazolyl-4-sulfonyl system. According to our previous investigation [3], the mechanism of this reaction involves formation of two intermediates, namely, the product of replacement of the N,N-dimethylamino group by a hydroxyamino group **12** and the unstable tricyclic system **13** formed as a result of the addition of a hydroxyamino group to the C(3)=C(4) bond in 3-cephem **12**.

In order to establish the role of the $–CH_2O-$ fragment in the 7-alkylidene sidechain of these cephems on their biological activity, we replaced this fragment by imino and carbonyl groups.

In the former case, we condensed the acetyl group in starting cephem **1** with 4-bromophenylhydrazine, leading to cephem **15** with a 2-*anti*-(4-bromophenylhydrazono)propylidene group at C-7, as indicated by the signal for the =CHC(Me) group at 6.97 ppm.



anti-**15** *anti*-**16**

In the latter case, we achieved our goal by acylation of the hydroxyimino group in cephem **3** using 2-bromobenzoyl chloride. In this case, only cephem **16** with *anti* configuration of the acyloxyimino group was isolated.

Biological screening of these products *in vitro* included determination of their cytotoxic properties towards to monolayer lines of HT-1080 (human fibrosarcoma) and MG-22A (murine hepatoma) malignant cells in comparison to normal 3T3 cells (murine embryonic fibroblasts). Coloration of the 3T3 fibroblasts by a neutral red dye permitted us to calculate the expected LD_{50} toxicity for the compounds tested using a special equation without recourse to experiments *in vivo* [4].

The screening data for esters **6a-k** given in Table 1 indicate that the biological properties of these compounds depend both on the structure of the aromatic fragment and configuration of the arylmethoxyimino and pyridylmethoxyimino groups in the 7-alkylidene substituent.

Thus, the presence of one or two halogen atoms in the benzene ring in esters **6b-i**, as a rule, enhances the cytotoxic effect of these compounds not only relative to malignant but also normal cells in comparison with the analogous effect shown by cephems **6a,j,k**, which have a phenyl or pyridyl group as the aromatic fragment. The *anti* or *syn* configuration of the arylmethoxyimino group also is a significant factor determining the selectivity of the cytotoxic action of the compounds tested, primarily in regard to only the malignant cells. The *syn* isomers of esters **6a,b,e,f** (with the exception of *syn*-**6g**) isolated as pure compounds proved less toxic in comparison with their *anti* isomers toward normal 3T3 cells than toward malignant HT-1080 and MG-22A cells. In the case of ester **6f**, the LD_{50} data show that this difference is two-fold, while in the case of ester **6a**, this difference is three-fold.

TABLE 1. Biological Properties of *tert*-Butyl Esters of 7*Z*-[2-(Aryl- and Pyridylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid **6***

Compound	LC_{50}, μg/ml							LD_{50}, mg/kg
	HT-1080			MG-22A			3T3	
	CV	MTT	TG_{100}	CV	MTT	TG_{100}	NR	
anti-**6a**	3	3	250	3	2	300	7	313
syn-**6a**	3	2	350	3	3	233	100	982
anti-**6b**	24	18	54	45	23	23	2	194
syn-**6b**	3	3	200	3	3	300	5	289
anti/syn-**6c**	3	3	250	2	2	250	5	294
anti/syn-**6d**	3	3	800	1	1	700	6	315
anti-**6e**	33	28	50	100	89	16	4	240
syn-**6e**	3	2	250	2	2	300	5	289
anti-**6f**	3	2	200	3	3	200	6	279
syn-**6f**	14	14	200	3	3	250	28	557
anti-**6g**	1.5	1.5	250	3	2	150	6	309
syn-**6g**	2	2	250	3	3	133	6	309
anti/syn-**6h**	0.8	1.3	200	1.8	3.2	350	5.8	309
anti/syn-**6i**	1.5	2.6	133	0.04	0.03	82	4.8	309
anti/syn-**6j**	2.1	0.8	350	0.8	0.5	400	6	671
anti/syn-**6k**	2.6	1.5	550	1.5	2.0	267	54	716

* LC_{50} is the concentration providing death of 50% of cells, CV indicates coloration by crystal violet, MTT indicates coloration by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide, TG_{100} is the specific NO generating activity of the compound, NR indicates coloration by Neutral Red, and LD_{50} is the calculated expected toxicity.

The data in Table 2 reflect the diminution of the biological effect following modification of the *tert*-butyl esters of 7*Z*-[2(arylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid through replacement of the sulfone moiety by a sulfide moiety and removal of the carboxyl group. In the former case, isomeric *anti*-**8b** and *syn*-**8b** show significantly weaker cytotoxic activity. However, in the latter case, independently of the configuration of the substituent at C-7, enhancement of the cytotoxic activity of cephems **10a-f** was observed, mainly, relative to normal cells reflected in a marked drop in the LD_{50} values.

According to the data in Table 3, the introduction of an N,N-dimethylaminomethylene group at C-2 of the cephem system leads to a significant increase in the cytotoxic selectivity of the corresponding derivatives of the *tert*-butyl ester of 7*Z*-[2-(arylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid **11a-f**. Comparison of the biological screening data of the *anti* and *syn* isomers indicates that better selectivity of ester **11a** is found for the *anti* isomer, while better selectivity of esters **11c,d,f** is found for the *syn* isomers. Opening of the cephem system at the C(3)=C(4) bond to give azetidinones **14a-c** is accompanied by weakening of the anticancer activity *in vitro*. Analogous properties were seen for cephem **15** with a 2-(4-bromophenylhydrazono)propylidene group at C-7. On the other hand, replacement of the methylene group by a carbonyl group in the 2-bromobenzyl moiety of cephem *anti*-**16** may hold promise for modification of biological activity.

The cytotoxic effect of most of the compounds tested is related to their capacity to generate nitric oxide in cellular media. As a rule, high toxicity accompanies a high level of NO generation and *vice versa*.

TABLE 2. Biological Properties of *tert*-Butyl Esters of 7*Z*-[2-(2-Bromobenzyloxyimino)propylidene]-3-methyl-3-cephem-4-carboxylic Acid **8** and 7*Z*-[2-(2-Arylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephems **10**

Compound	LC_{50}, μg/ml							LD_{50}, mg/kg
	HT-1080			MG-22A			3T3	
	CV	MTT	TG_{100}	CV	MTT	TG_{100}	NR	
anti-**8b**	60	56	9	70	63	11	>1000	2812
syn-**8b**	100	>100	5	81	>100	7	922	2714
anti-**10a**	2	1	400	1	2	300	4	233
syn-**10a**	2	2	250	2	1	250	5	234
anti-**10b**	2	2	350	2	2	450	3	210
syn-**10b**	0.2	0.4	250	0.2	0.3	100	2	170
anti-**10c**	2	2	300	1	1	300	5	272
syn-**10c**	0.6	0.5	300	0.3	0.6	300	2	183
anti-**10d**	1	1	300	0.3	0.3	300	3	235
syn-**10d**	1	2	500	2	1	350	3	235
anti-**10e**	1	1	200	2	2	150	2	160
syn-**10e**	0.2	0.7	200	0.2	0.3	60	2	160
anti-**10f**	0.2	0.2	200	0.3	0.3	120	2	146
syn-**10f**	0.2	0.3	100	0.2	0.3	100	5	219

TABLE 3. Biological Properties of Cephems **11a-f, 15, 16,** and Azetidinones **14a-c**

Compound	LC_{50}, μg/ml							LD_{50}, mg/kg
	HT-1080			MG-22A			3T3	
	CV	MTT	TG_{100}	CV	MTT	TG_{100}	NR	
anti-**11a**	3	3	1000	2	2	1000	87	1003
syn-**11a**	3	3	500	3	2	150	12	417
anti-**11b**	90	37	200	3	3	37	534	2380
anti-**11c**	10	10	67	3	3	200	100	1161
syn-**11c**	10	11	175	2	2	300	920	2961
anti-**11d**	3	3	500	1	2	300	30	639
syn-**11d**	3	3	800	2	2	850	151	1335
anti-**11e**	4	4	100	2	2	300	100	1072
syn-**11e**	1	3	325	1	1	533	72	965
anti-**11f**	3	3	300	4	3	64	23	572
syn-**11f**	10	22	250	4	6	250	100	1091
anti-**14a**	32	30	200	23	29	350	167	1273
anti-**14b**	7	10	450	3	6	267	16	512
anti-**14c**	21	20	150	19	17	300	100	1080
anti-**15**	21	26	250	49	49	19	100	1072
anti-**16**	1	1	150	1	<1	200	13	432

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian Mercury-200 spectrometer at 200 MHz in $CDCl_3$ for **6, 8, 11, 14,** and **16**, in DMSO-d_6 for **15**, and on a Varian Mercury-400 spectrometer at 400 MHz in DMSO-d_6 for **3** with HMDS as the internal standard (δ 0.05 ppm). The elemental analysis was carried out on a Carlo Erba 1108 analyzer. The ESI-MS mass spectra were taken on a Micromass Quatro Micro™ API inductively coupled

plasma mass spectrometer in MeCN for **6, 10,** *anti*-**11a**, *anti*-**11b**, *anti*-**11f, 15,** and **16,** MeOH + HCO_2H for *syn*-**11a**, and MeOH for **11c-11e** and **14-16**. The reaction course was monitored by thin-layer chromatography on Merck Kieselgel plates with development in UV light. Preparative column chromatography was carried out using Merck Kieselgel (0.060-0.200 mm). The reagents and materials used in these experiments were obtained from Acros and Aldrich.

The 2D spectra were taken with a 4096 × 1024 database, which provided τ_{2max} = 250 msec for ^1H for recording along the *F*2 axis and τ_{1max} = 100 msec along the *F*1 axis. In order to improve the signal-to-noise ratio, the data matrix prior to the Fourier transformation was twice supplemented with zeros and multiplied by the cosine function. The mixing time in the 2D-NOESY was 1 sec.

The optical density in the biological tests carried out in a 96-well panel was determined on a Tetretek Multiscan MCC/340 horizontal spectrophotometer.

3:1 Mixture of *tert*-Butyl Ester of 7*Z*-[2-(*anti*-Hydroxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-3) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-Hydroxyimino)propylidene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*syn*-3). Hydroxylamine hydrochloride (188 mg, 2.7 mmol) and sodium acetate (224 mg, 2.7 mmol) were added to a solution of *tert*-butyl ester 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (715 mg, 2.1 mmol) in methanol (30 ml). The reaction mixture was stirred for 24 h at room temperature and evaporated at reduced pressure. The residue was fractionated on a silica gel column. The fractions with R_f 0.34 (1:4 ethyl acetate–hexane) gave 495 mg (66%) mixture of *anti*-**3** and *syn*-**3**. ^1H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**3**) 1.46 (9H, s, C_4H_9); 1.92 (3H, s, CH_3); 2.02 (3H, s, CH_3C=N); 4.18-4.40 (2H, m, SO_2CH_2); 6.20 (1H, br. s, H-6); 6.88 (1H, d, ^4J = 1.2, =CHC(Me)=N); 12.32 (1H, s, OH); *syn*-**3**) 1.46 (9H, s, C_4H_9); 1.92 (3H, s, CH_3); 2.10 (3H, s, CH_3C=N); 4.18-4.40 (2H, m, SO_2CH_2); 6.19 (1H, s, H-6); 7.41 (1H, d, ^4J = 1.2, =CHC(Me)=N); 11.32 (1H, s, OH). Found, %: C 50.65; H 5.78; N 7.91. $C_{15}H_{20}N_2O_6S$. Calculated, %: C 50.55; H 5.66; N 7.87.

Preparation of *tert*-Butyl Esters of 7*Z*-[2-(Arylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acids 6a-g. Method A. Arylmethoxyamine hydrochloride **2a-g** (3.26 mmol) and sodium acetate (267 mg, 3.26 mmol) were added to *tert*-butyl ester of 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (857 mg, 2.51 mmol) in methanol (30 ml). The reaction mixture was stirred for 24 h at room temperature and evaporated at reduced pressure. The residue was fractionated on a silica gel column to give cephems **6a-g**.

2:1 Mixture of *tert*-Butyl Ester of 7*Z*-[2-*anti*-(Benzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-6a) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(Benzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*syn*-6a) was obtained in 89% yield using benzyloxyamine hydrochloride. Mass spectrum, *m/z*: 469 [M+Na^+]. Found, %: C 58.90; H 6.13; N 6.57. $C_{22}H_{26}N_2O_6S$. Calculated, %: C 59.18; H 5.87; N 6.27.

The fractions with R_f 0.71 (1:1 ethyl acetate–hexane) gave *anti*-**6a**. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.10 (3H, s, CH_3C=N); 3.64, 3.87 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.25 (2H, s, CH_2Ph); 5.37 (1H, br. s, H-6); 6.90 (1H, d, ^4J = 1.2, =CHC(Me)=N); 7.31-7.40 (5H, m, C_6H_5).

The fractions with R_f 0.63 (1:1 ethyl acetate–hexane) gave *syn*-**6a**. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H); 2.07 (3H, s, CH_3); 2.19 (3H, s, CH_3C=N); 3.64, 3.87 (2H, two d, AB system, ^4J = 18, SO_2CH_2); 5.18 (2H, s, CH_2Ph); 5.28 (1H, br. s, H-6); 7.56 (1H, d, ^4J = 1.2, =CHC(Me)=N); 7.31-7.40 (5H, m, C_6H_5).

4:1 Mixture of *tert*-Butyl Ester of 7*Z*-[2-*anti*-(2-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-6b) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(2-Bromobenzyl-oxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*syn*-6b) was obtained in 75% yield using 2-bromobenzyloxyamine hydrochloride.

The fractions with R_f 0.61 (1:1 ethyl acetate–hexane) gave *anti*-**6b** in 60% yield. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.14 (3H, s, CH_3C=N); 3.65, 3.89 (2H, two d, AB system,

^2J = 18, SO_2CH_2); 5.35 (2H, s, CH_2Ph); 5.39 (1H, br. s, H-6); 6.90 (1H, d, ^4J = 1.2, =CHC(Me)=N); 7.10-7.44 (3H, m, H-4, H-5, H-6 C_6H_4); 7.57 (1H, d, ^3J = 7.3, H-3 C_6H_4). Mass spectrum, *m/z*: 547/549 [M+Na^+].

The fractions with R_f 0.53 (1:1 ethyl acetate–hexane) gave *syn*-**6b** in 15% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.20 (3H, s, CH_3C=N); 3.65, 3.89 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.27 (2H, s, CH_2Ph); 5.35 (1H, br. s, H-6); 7.11-7.44 (3H, m, H-4, H-5, H-6 C_6H_4); 7.56 (1H, d, ^3J = 7.8, H-3 C_6H_4); 7.62 (1H, d, ^4J = 1.2, =CHC(Me)=N). Mass spectrum: 547/549 [M+Na^+].

2:3 Mixture of *tert*-Butyl Ester of 7*Z*-[2-*anti*-(3-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-6c) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(3-bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (*syn*-6c) was obtained in 64% yield using 3-bromobenzyloxyamine hydrochloride. The fractions with R_f 0.70 (1:1 ethyl acetate–hexane) gave an isomer mixture of *anti*-**6c** and *syn*-**6c**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**6c**) 1.53 (9H, s, C_4H_9); 2.06 (3H, s, CH_3); 2.10 (3H, s, CH_3C=N); 3.64, 3.89 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.20 (2H, s, CH_2Ph); 5.37 (1H, br. s, H-6); 6.87 (1H, d, ^4J = 1.2, =CHC(Me)=N); 7.16-7.53 (4H, m, C_6H_4); *syn*-**6c**) 1.53 (9H, s, C_4H_9); 2.06 (3H, s, CH_3); 2.18 (3H, s, CH_3C=N); 3.64, 3.87 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.12 (2H, s, CH_2Ph); 5.31 (1H, br. s, H-6); 7.16-7.53 (4H, m, C_6H_4); 7.54 (1H, d, ^4J = 1.2, =CHC(Me)=N). Found, %: C 49.99; H 4.55; N 5.16. $C_{22}H_{25}BrN_2O_6S$. Calculated, %: C 50.29; H 4.80; N 5.33.

Mixture of *tert*-Butyl Ester of 7*Z*-[2-*anti*-(4-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-6d) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(4-bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (*syn*-6d) was obtained in 62% yield using 4-bromobenzyloxyamine. The fractions with R_f 0.70 (1:1 ethyl acetate–hexane) gave an isomer mixture of *anti*-**6d** and *syn*-**6d**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**6d**) 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.09 (3H, s, CH_3C=N); 3.65, 3.90 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.19 (2H, s, CH_2Ph); 5.39 (1H, br. s, H-6); 6.87 (1H, d, ^4J = 1.5, =CHC(Me)=N); 7.23 (2H, d, ^3J = 8.8, H-2, H-6 C_6H_4); 7.48 (2H, d, ^3J = 8.8, H-3, H-5 C_6H_4); *syn*-**6d**) 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.17 (3H, s, CH_3C=N); 3.65, 3.90 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.11 (2H, s, CH_2Ph); 5.34 (1H, br. s, H-6); 7.23 (2H, d, ^3J = 8.8, H-2, H-6 C_6H_4); 7.48 (2H, d, ^3J = 8.8, H-3, H-5 C_6H_4); 7.54 (1H, d, ^4J = 1.4, =CHC(Me)=N). Mass spectrum, *m/z*: 548 [M+Na^+]. Found, %: C 50.31; H 4.70; N 5.33. $C_{22}H_{25}BrN_2O_6S$. Calculated, %: C 50.29; H 4.80; N 5.33.

Mixture of *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-chlorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*anti*-6e) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(2-chlorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-6e) was obtained using 2-chlorobenzyloxyamine hydrochloride.

The fractions with R_f 0.63 (1:1 ethyl acetate–hexane) gave *anti*-**6e** in 43% yield; mp 190-192°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.13 (3H, s, CH_3C=N); 3.64, 3.88 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.37 (2H, s, CH_2Ph); 5.40 (1H, br. s, H-6); 6.89 (1H, d, ^4J = 1.3, =CHC(Me)=N); 7.22-7.43 (4H, m, C_6H_4). Mass spectrum, *m/z*: 503 [M+Na^+].

The fractions with R_f 0.57 (1:1 ethyl acetate–hexane) gave *syn*-**6e** in 30% yield; mp 168-170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.19 (3H, s, CH_3C=N); 3.66, 3.90 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.30 (2H, s, CH_2Ph); 5.33 (1H, br. s, H-6); 7.22-7.44 (4H, m, C_6H_4); 7.61 (1H, d, ^4J = 1.4, =CHC(Me)=N). Mass spectrum, *m/z*: 503 [M+Na^+].

Mixture of *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-fluorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*anti*-6f) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(2-fluorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-6f) was obtained using 2-fluorobenzyloxyamine.

The fractions with R_f 0.63 (1:1 ethyl acetate–hexane) gave *anti*-**6f** in 60% yield; mp 162-166°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.06 (3H, s, CH_3); 2.08 (3H, s, CH_3C=N); 3.64, 3.88 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.32 (2H, s, CH_2Ph); 5.41 (1H, br. s, H-6); 6.89 (1H, d, ^4J = 1.3, =CHC(Me)=N); 6.99-7.44 (4H, m, C_6H_4). Mass spectrum: 487 [M+Na^+].

The fractions with R_f 0.54 (1:1 ethyl acetate–hexane) give *syn*-**6f** in 24% yield; mp 167-172°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.18 (3H, s, CH_3C=N); 3.65, 3.89 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.24 (2H, s, CH_2Ph); 5.31 (1H, br. s, H-6); 6.99-7.45 (4H, m, C_6H_4); 7.56 (1H, d, ^4J = 1.3, =CHC(Me)=N). Mass spectrum, *m/z*: 487 [M+Na$^+$].

Mixture of *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-trifluoromethylbenzyloxyimino)-propylidene]-3-cephem-4-carboxylic Acid (*anti*-6g) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(2-trifluoromethylbenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-6g) was obtained using 2-trifluoromethylbenzyloxyamine.

The fractions with R_f 0.66 (1:1 ethyl acetate–hexane) gave *anti*-**6f** in 48% yield; mp 152-156°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.06 (3H, s, CH_3); 2.12 (3H, s, CH_3C=N); 3.64, 3.88 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.40 (1H, br. s, H-6); 5.46 (2H, s, CH_2Ph); 6.89 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.35-7.48 (2H, m, H-5, H-6 C_6H_4); 7.54 (1H, m, H-4 C_6H_4); 7.66 (1H, d, ^3J = 7.3, H-3 C_6H_4). Mass spectrum, *m/z*: 537 [M+Na$^+$].

The fractions with R_f 0.54 (1:1 ethyl acetate–hexane) gave *syn*-**6g** in 31% yield; mp 155-158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.20 (3H, s, CH_3C=N); 3.66, 3.90 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.33 (1H, br. s, H-6); 5.39 (2H, s, CH_2Ph); 7.35-7.49 (2H, m, H-5, H-6 C_6H_4); 7.51-7.59 (1H, m, H-4 C_6H_4); 7.62 (1H, d, ^4J = 1.5, =CHC(Me)=N); 7.66 (1H, d, ^3J = 7.8, H-3 C_6H_4). Mass spectrum, *m/z*: 537 [M+Na$^+$].

Preparation of *tert*-Butyl Esters of 7*Z*-[2-(Aryl- and 7*Z*-(2-Pyrimidylmethoxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acids 6h-k. Method B. 60% NaH (34 mg, 0.85 mmol) and arylmethyl bromide **5h,i** or pyridylmethyl bromide **5j,k** (0.20 mmol) were added to a solution of mixture of *anti* and *syn* isomers of the *tert*-butyl ester of 7*Z*-[2-(hydroxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (60 mg, 0.17 mmol) in DMF (5 ml) at 0°C. The mixture was warmed to room temperature, stirred for 3 h, then diluted with 50 ml ethyl acetate, and washed with two portions of 5% aqueous NaCl (50 ml). The organic layer was dried over anhydrous sodium sulfate, and evaporated. The residue was fractionated on a silica gel column to give cephems **6h-k**.

1:6 Mixture of *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(2,6-Dichlorobenzyloxyimino)-propylidene]-3-cephem-4-carboxylic Acid (*anti*-6h) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(2,6-dichlorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-6h) was obtained using 2,6-dichlorobenzyl bromide. The fractions with R_f 0.22 (1:4 ethyl acetate–hexane) gave the ester mixture in 55% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**6h**) 1.53 (9H, s, C_4H_9); 2.05 (3H, s, CH_3); 2.10 (3H, s, CH_3C=N); 3.63, 3.88 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.30 (2H, s, CH_2Ph); 5.53 (1H, br. s, H-6); 6.90 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.16-7.36 (3H, m, C_6H_3); *syn*-**6h**) 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.19 (3H, s, CH_3C=N); 3.64, 3.88 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.30 (2H, s, CH_2Ph); 5.53 (1H, br. s, H-6); 7.16-7.36 (3H, m, C_6H_3); 7.54 (1H, d, ^4J = 1.4, =CHC(Me)=N). Found, %: C 51.35; H 4.72; N 5.36. $C_{22}H_{24}Cl_2N_2O_6S$. Calculated, %: C 51.27; H 4.69; N 5.44.

4:1 Mixture of *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(3,4-dichlorobenzyloxyimino)-propylidene]-3-cephem-4-carboxylic Acid (*anti*-6i) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(3,4-dichlorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-6i) was obtained using 3,4-dichlorobenzyl bromide. The fractions with R_f 0.20 (4:1 ethyl acetate–hexane) gave the ester mixture in 48% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**6i**) 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.09 (3H, s, CH_3C=N); 3.64, 3.87 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.09 (2H, s, CH_2Ph); 5.18 (1H, br. s, H-6); 6.85 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.14-7.25 (1H, m, H-2 C_6H_3); 7.37-7.54 (2H, m, H-5, H-6 C_6H_3); *syn*-**6i**) 1.53 (9H, s, C_4H_9); 2.07 (3H, s, CH_3); 2.17 (3H, s, CH_3C=N); 3.64, 3.87 (2H, two d, ^2J = 18, SO_2CH_2); 5.31 (1H, br. s, H-6); 5.35 (2H, s, CH_2Ph); 7.14-7.25 (1H, m, H-2 C_6H_3); 7.37-7.54 (2H, m, H-5, H-6 C_6H_3); 7.54 (1H, d, ^4J = 1.4, =CHC(Me)=N). Found, %: C 51.42; H 4.75; N 5.50. $C_{22}H_{24}Cl_2N_2O_6S$. Calculated, %: C 51.27; H 4.69; N 5.44.

2:3 Mixture of *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(3-pyridylmethoxyimino)-propylidene]-3-cephem-4-carboxylic Acid (*anti*-6j) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(3-pyridylmethoxyimino)propylidene]-3-cephem-4-carboxylic acid (*syn*-6j) was obtained using 3-pyridylmethyl chloride. The fractions with R_f 0.08 (3:1 ethyl acetate–hexane) gave the ester mixture in 15% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**6j**) 1.53 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.08 (3H, s, CH_3C=N); 3.64, 3.96 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.19 (2H, s, CH_2Py); 5.28 (1H, br. s, H-6); 6.82 (1H, d, ^4J = 1.0, =CHC(Me)=N); 7.30-7.45 (1H, m, H-5 Py); 7.70-7.85 (1H, m, H-4 Py); 8.50-8.80 (2H, br. s, H-2, H-6 Py); *syn*-**6j**) 1.53 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.17 (3H, s, CH_3C=N); 3.64, 3.90 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.30 (1H, br. s, H-6); 5.37 (2H, s, CH_2Py); 7.30-7.45 (1H, m, H-5 Py); 7.52 (1H, d, ^4J = 1.0, =CHC(Me)=N); 7.70-7.85 (1H, m, H-4 Py); 8.50-8.80 (2H, br. s, H-2, H-6 Py). Found, %: C 56.51; H 5.73; N 9.42. $C_{21}H_{25}N_3O_6S$. Calculated, %: C 56.36; H 5.63; N 9.39.

1:2 Mixture of *tert*-Butyl Ester of 3-methyl-1,1-dioxo-7*Z*-[2-*anti*-(4-pyridylmethoxyimino)propylidene]-3-cephem-4-carboxylic Acid (*anti*-6k) and *tert*-Butyl Ester of 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(4-pyridylmethoxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-6k) was obtained using 4-pyridylmethyl chloride.

The fractions with R_f 0.08 (3:1 ethyl acetate–hexane) gave the ester mixture in 15% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *anti*-**6k**) 1.53 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.15 (3H, s, CH_3C=N); 3.65, 3.85 (2H, two d, AB system, ^3J = 18, SO_2CH_2); 5.21 (1H, br. s, H-6); 5.36 (2H, s, CH_2Py); 6.84 (1H, d, ^4J = 1.0, =CHC(Me)=N); 7.33 (2H, br. s, H-3, H-5 Py); 8.61 (2H, br. s, H-2, H-6 Py); *syn*-**6k**) 1.53 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 2.20 (3H, s, CH_3C=N); 3.66, 3.91 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.21 (1H, br. s, H-6); 5.36 (2H, s, CH_2Py); 7.33 (2H, br. s, H-3, H-5 Py); 7.60 (1H, d, ^4J = 1.0, =CHC(Me)=N); 8.61 (2H, br. s, H-2, H-6 Py). Found, %: C 56.47; H 5.70; N 9.45. $C_{21}H_{25}N_3O_6S$. Calculated, %: C 56.36; H 5.63; N 9.39.

2:1 Mixture of *tert*-Butyl Ester of 7*Z*-[2-*anti*-(2-Bromobenzyloxyimino)propylidene]-3-methyl-3-cephem-4-carboxylic Acid (*anti*-8b) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(2-Bromobenzyloxyimino)-propylidene]-3-methyl-3-cephem-4-carboxylic Acid (*syn*-8b) was obtained by Method A from the *tert*- butyl ester of 7*Z*-acetylmethylene-3-methyl-3-cephem-4-carboxylic acid **7** and 2-bromobenzyloxyamine hydrochloride. Found, %: C 53.67; H 5.20; N 5.75. $C_{22}H_{25}BrN_2O_4S$. Calculated, %: C 53.55; H 5.11; N 5.68.

The fractions with R_f 0.57 (1:3 ethyl acetate–hexane) gave *anti*-**8b** in 41% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.03 (3H, s, CH_3); 2.07 (3H, s, CH_3C=N); 3.14, 3.50 (2H, two d, AB system, ^2J = 18, SCH_2); 5.26 (1H, br. s, H-6); 5.31 (2H, s, CH_2Ph); 6.68 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.12-7.43 (3H, m, H-4, H-5, H-6 C_6H_4); 7.56 (1H, d, ^3J = 7.8, H-3 C_6H_4).

The fractions with R_f 0.48 (1:3 ethyl acetate–hexane) gave *syn*-**8b** in 21% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.03 (3H, s, CH_3); 2.13 (3H, s, CH_3C=N); 3.18, 3.53 (2H, two d, AB system, ^2J = 18, SCH_2); 5.24 (2H, s, CH_2Ph); 5.27 (1H, br. s, H-6); 7.10-7.41 (3H, m, H-4, H-5, H-6 C_6H_4); 7.45 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.55 (1H, d, ^3J = 8.8, H-3 C_6H_4).

7*Z*-[2-*anti*-(Benzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*anti*-10a) and 7*Z*-[2-*syn*-(Benzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*syn*-10a) were obtained by Method A from 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem and benzyloxyamine hydrochloride in 47% yield. Found, %: C 59.03; H 5.32; N 8.15. $C_{17}H_{18}N_2O_4S$. Calculated, %: C 58.94; H 5.24; N 8.09.

The fractions with R_f 0.68 (1:1 ethyl acetate–hexane) gave *anti*-**10a** in 28% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.11 (3H, s, CH_3C=N); 3.46, 3.96 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 5.25 (2H, s, CH_2Ph); 5.38 (1H, br. s, H-6); 6.55 (1H, br. s, H-4); 6.92 (1H, d, ^4J = 1.5, =CHC(Me)=N); 7.31-7.41 (5H, m, C_6H_5).

The fractions with R_f 0.60 (1:1 ethyl acetate–hexane) gave *syn*-**10a** in 19% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.19 (3H, s, CH_3C=N); 3.46, 3.93 (2H, two d, AB system, ^2J = 18.1, SO_2CH_2); 5.17 (2H, s, CH_2Ph); 5.26 (1H, br. s, H-6); 6.55 (1H, br. s, H-4); 7.31-7.41 (5H, m, C_6H_5); 7.54 (1H, d, ^4J = 1.4, =CHC(Me)=N).

Mixture of 7*Z*-[2-*anti*-(2-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*anti*-10b) and 7*Z*-[2-*syn*-(2-bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*syn*-10b) was obtained from 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem and 2-bromobenzyloxyamine hydrochloride.

The fractions with R_f 0.48 (1:1 ethyl acetate–hexane) gave *anti*-**10b** in 34% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.15 (3H, s, CH_3C=N); 3.45, 3.95 (2H, two d, AB system, ^2J = 18.1, SO_2CH_2); 5.35 (2H, s, CH_2Ph); 5.39 (1H, br. s, H-6); 6.54 (1H, br. s, H-4); 6.91 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.12-7.41 (3H, m, H-4, H-5, H-6 C_6H_4); 7.56 (1H, d, ^3J = 7.9, H-3 C_6H_4). Mass spectrum: 447/449 [M+Na$^+$].

The fractions with R_f 0.37 (1:1 ethyl acetate–hexane) gave *syn*-**10b** in 24% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (3H, s, CH_3); 2.20 (3H, s, CH_3C=N); 3.46, 3.96 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 5.27 (2H, s, CH_2Ph); 5.32 (1H, br. s, H-6); 6.56 (1H, br. s, H-4); 7.12-7.41 (3H, m, H-4, H-5, H-6 C_6H_4); 7.56 (1H, d, ^3J = 8.3, H-3 C_6H_4); 7.60 (1H, d, ^4J = 1.0, =CHC(Me)=N). Mass spectrum, *m/z*: 447/449 [M+Na$^+$].

Mixture of 7*Z*-[2-*anti*-(3-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*anti*-10c) and 7*Z*-[2-*syn*-(3-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*syn*-10c) was obtained in 60% yield by Method A from 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem and 3-bromobenzyloxyamine hydrochloride. Found, %: C 48.21; H 4.11; N 6.64. $C_{17}H_{17}BrN_2O_4S$. Calculated, %: C 48.01; H 4.03; N 6.59.

The fractions with R_f 0.48 (1:1 ethyl acetate–hexane) gave *anti*-**10c** in 37% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.11 (3H, s, CH_3C=N); 3.46, 3.96 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 5.21 (2H, s, CH_2Ph); 5.36 (1H, br. s, H-6); 6.55 (1H, br. s, H-4); 6.88 (1H, d, ^4J = 1.4, =CHC(Me)=N); 7.17-7.32 (2H, m, H-5, H-6 C_6H_4); 7.44 (1H, d, ^3J = 7.4, H-4 C_6H_4); 7.51 (1H, s, H-2 C_6H_4).

The fractions with R_f 0.36 (1:1 ethyl acetate–hexane) gave *syn*-**10c** in 23% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.18 (3H, s, CH_3C=N); 3.46, 3.95 (2H, two d, AB system, ^2J = 18.1, SO_2CH_2); 5.11 (2H, s, CH_2Ph); 5.27 (1H, s, H-6); 6.55 (1H, br. s, H-4); 7.16-7.32 (2H, m, H-5, H-6 C_6H_4); 7.44 (1H, d, ^3J = 7.3, H-4 C_6H_4); 7.49 (1H, br. s, =CHC(Me)=N); 7.51 (1H, s, H-2 C_6H_4).

Mixture of 7*Z*-(2-*anti*-(4-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*anti*-10d) and 7*Z*-(2-*syn*-(4-Bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem (*syn*-10d) was obtained in 61% yield from 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem and 4-bromobenzyloxyamine hydrochloride. Found, %: C 48.15; H 4.17; N 6.63. $C_{17}H_{17}BrN_2O_4S$. Calculated %: C 48.01; H 4.03; N 6.59.

The fractions with R_f 0.48 (1:1 ethyl acetate–hexane) gave *anti*-**10d** in 36% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.10 (3H, s, CH_3C=N); 3.45, 3.94 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 5.19 (2H, s, CH_2Ph); 5.36 (1H, br. s, H-6); 6.55 (1H, br. s, H-4); 6.88 (1H, d, ^4J = 1.5, =CHC(Me)=N); 7.23 (2H, d, ^3J = 8.3, H-2, H-6 C_6H_4); 7.48 (2H, d, ^3J = 8.3, H-3, H-5 C_6H_4).

The fractions with R_f 0.36 (1:1 ethyl acetate–hexane) gave *syn*-**10d** in 25% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (3H, s, CH_3); 2.18 (3H, s, CH_3C=N); 3.46, 3.94 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 5.11 (2H, s, CH_2Ph); 5.27 (1H, br. s, H-6); 6.55 (1H, br. s, H-4); 7.22 (2H, d, ^3J = 8.3, H-2, H-6 C_6H_4); 7.48 (2H, d, ^3J = 8.3, H-3, H-5 C_6H_4); 7.53 (1H, d, ^4J = 1.4, =CHC(Me)=N).

Mixture of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-chlorobenzyloxyimino)propylidene]-3-cephem (*anti*-10e) and 3-Methyl-1,1-dioxo-7*Z*-[2-*syn*-(2-chlorobenzyloxyimino)propylidene-3-cephem (*syn*-10e) was obtained by Method A from 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem and 2-chlorobenzyloxyamine hydrochloride.

The fractions with R_f 0.43 (1:1 ethyl acetate–hexane) gave *anti*-**10e** in 64% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.79 (1H, s, CH_3); 2.14 (3H, s, CH_3C=N); 3.45, 3.95 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.36 (2H, s, CH_2Ph); 5.40 (1H, br. s, H-6); 6.54 (1H, br. s, H-4); 6.90 (1H, d, ^4J = 1.5, =CHC(Me)=N); 7.22-7.42 (4H, m, C_6H_4). Mass spectrum, *m/z*: 381/383 [M$^+$].

The fractions with R_f 0.31 (1:1 ethyl acetate–hexane) gave *syn*-**10e** in 24% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.81 (3H, s, CH_3); 2.20 (3H, s, CH_3C=N); 3.46, 3.95 (2H, two d, AB system, ^2J = 18, SO_2CH_2);

5.29 (2H, s, CH_2Ph); 5.37 (1H, br. s, H-6); 6.56 (1H, br. s, H-4); 7.22-7.42 (4H, m, C_6H_4); 7.58 (1H, d, ^4J = 1.4, =CHC(Me)=N). Mass spectrum, *m/z*: 381/383 [M^+].

Mixture of 3-Methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-fluorobenzyloxyimino)propylidene]-3-cephem (*anti*-10f) and 3-methyl-1,1-dioxo-7*Z*-[2-*syn*-(2-fluorobenzyloxyimino)propylidene]-3-cephem (*syn*-10f) was obtained by Method A from 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-3-cephem and 2-fluorobenzyloxyamine hydrochloride.

The fractions with R_f 0.40 (1:1 ethyl acetate–hexane) gave *anti*-**10f** in 73% yield; mp 120-122°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.79 (3H, s, CH_3); 2.09 (3H, s, CH_3C=N); 3.44, 3.95 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.32 (2H, s, CH_2Ph); 5.40 (1H, br. s, H-6); 6.54 (1H, br. s, H-4); 6.90 (1H, d, ^4J = 1.5, =CHC(Me)=N); 6.99-7.44 (4H, m, C_6H_4). Mass spectrum, *m/z*: 387/388 [M+Na^+].

The fractions with R_f 0.33 (1:1 ethyl acetate–hexane) gave *syn*-**10f** in 24% yield; mp 122-124°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.80 (3H, s, CH_3); 2.19 (3H, s, CH_3C=N); 3.46, 3.95 (2H, two d, AB system, ^2J = 18, SO_2CH_2); 5.24 (1H, s, CH_2Ph); 5.29 (1H, br. s, H-6); 6.55 (1H, br. s, H-4); 6.99-7.44 (4H, m, C_6H_4); 7.53 (1H, d, ^4J = 1.3, =CHC(Me)=N). Mass spectrum, *m/z*: 387/388 [M+Na^+].

Preparation of *tert*-Butyl Esters of 7*Z*-[2-(Arylmethoxyimino)propylidene]-2-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acids 11a-f. Typical procedure. A mixture of oxalyl chloride (234 μl, 2.687 mmol) and DMF (209 μl, 2.687 mmol) in acetonitrile (15 ml) was added to a stirred suspension of *tert*-butyl ester of 7Z-[2-(arylmethoxyimino)-propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (0.672 mmol) in acetonitrile (15 ml) at -5°C in an argon atmosphere. The reaction mixture was stirred for 1.5 h at 0°C, neutralized by adding dry pyridine (217 μl, 2.687 mmol), diluted by adding 100 ml 5% aqueous NaCl, and extracted with two 30-ml portions of ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure. The residue was fractionated on a silica gel column with ethyl acetate–hexane as the eluent (the solvent ratio was varied from 1:10 to 1:2) to give cephems **11a-f**.

***tert*-Butyl Ester of 7*Z*-[2-*anti*-(Benzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-11a) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(Benzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (*syn*-11a)** were obtained from a mixture of the *anti* and *syn* isomers of the *tert*-butyl ester of 7*Z*-[2-(benzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.60 (1:1 ethyl acetate–hexane) gave 195 mg (58%) of a 4:1 mixture of 2*E*- and 2*Z*-isomers of *anti*-**11a**; mp 96-98°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.14 (3H, s, CH_3); 2.23 (3H, s, CH_3C=N); 3.04 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.23 (2H, s, CH_2Ph); 5.42 (1H, ^4J = 1.0, H-6); 6.85 (1H, br. s, =CHC(Me)=N); 6.93 (0.2H, s, =$CHNMe_2$ 2*Z*-isomer); 7.23 (0.8H, s, =$CHNMe_2$ 2*E*-isomer); 7.31-7.40 (5H, m, C_6H_5). Mass spectrum, *m/z*: 399 [M^+-$CO_2C(CH_3)_3$].

The fractions with R_f 0.48 (1:1 ethyl acetate–hexane) gave 88 mg (26%) of a 4:1 mixture of a 2*E*/2*Z*-isomers of *syn*-**11a**; mp 90-92°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (9H, s, C_4H_9); 2.21 (3H, s, CH_3); 2.22 (3H, s, CH_3C=N); 3.05 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.33 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.16 (2H, s, CH_2Ph); 5.34 (1H, s, H-6); 6.95 (0.2H, s, =$CHNMe_2$ 2*Z*-isomer); 7.25 (0.8H, s, =$CHNMe_2$ 2*E*-isomer); 7.31-7.40 (5H, m, C_6H_5); 7.50 (1H, s, =CHC(Me)=N). Mass spectrum, *m/z*: 399 [M^+-$CO_2C(CH_3)_3$].

***tert*-Butyl Ester of 7*Z*-[2-*anti*-(2-Bromobenzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-11b) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(2-bromobenzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (*syn*-11b)** were obtained using a mixture of the *anti* and *syn* isomers of the *tert*-butyl ester of 7*Z*-[2-(2-bromobenzyloxyimino]propylidene-2(*E/Z*)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.78 (2:1 ethyl acetate–hexane) gave 33 mg (30%) of a 4:1 mixture of 2*E*- and 2*Z*-isomers of *anti*-**11b**; mp 134-136°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.18 (3H, s, CH_3); 2.23 (3H, s, CH_3C=N); 3.05 (4.8H, s, $N(CH_3)_2$) 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.32 (2H,

s, CH_2Ph); 5.42 (1H, d, $^4J = 1.0$, H-6); 6.84 (1H, d, $^4J = 1.0$, =CHC(Me)=N); 6.93 (0.2H, s, $=CHNMe_2$ 2*Z*- isomer); 7.09-7.44 (3.8H, m, $=CHMe_2$ 2*E*-isomer, H-4, H-5, H-6 C_6H_4); 7.56 (1H, d, $^3J = 7.8$, H-3 C_6H_4). Mass spectrum, *m/z*: 602/604 [M^+-$CO_2C(CH_3)_3$].

The fractions with R_f 0.62 (2:1 ethyl acetate–hexane) gave 21 mg (19%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *syn*-**11b**; mp 130-132°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.22 (3H, s, CH_3); 2.22 (3H, s, CH_3C=N); 3.05 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.33 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.25 (2H, s, CH_2Ph); 5.36 (1H, s, H-6); 6.96 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.10-7.44 (3.8H, m, $=CHMe_2$ 2*E*-isomer, H-4, H-5, H-6 C_6H_4); 7.54 (1H, d, $^3J = 7.4$, H-3 C_6H_4); 7.55 (1H, s, =CHC(Me)=N). Mass spectrum, *m/z*: 602/604 [M^+-$CO_2C(CH_3)_3$].

***tert*-Butyl Ester of 7*Z*-[2-*anti*-(3-Bromobenzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylamino-methylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-11c) and *tert*-Butyl Ester of 7*Z*-[2-syn-(3-Bromobenzyloxyimino)propylidene]-2(E/Z)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*syn*-11c)** were obtained using a mixture of *anti* and *syn* isomers of the *tert*-butyl ester of 7*Z*-[2-(3-bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.28 (1:2 ethyl acetate–hexane) gave 40 mg (36%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *anti*-**11c**; mp 82-84°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.14 (3H, s, CH_3); 2.22 (3H, s, CH_3C=N); 3.04 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.17 (2H, s, CH_2Ph); 5.41 (1H, s, H-6); 6.82 (1H, s, =CHC(Me)=N); 6.94 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.17-7.33 (2.8H, m, $=CHMe_2$ 2*E*-isomer); H-5, H-6 C_6H_4); 7.44 (1H, d, $^3J = 7.4$, H-4 C_6H_4); 7.51 (1H, br. s, H-2 C_6H_4). Mass spectrum: 603 [M+Na^+].

The fractions with R_f 0.48 (1:2 ethyl acetate–hexane) gave 21 mg (19%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *syn*-**11c**; mp 73-75°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.20 (3H, s, CH_3); 2.22 (3H, s, CH_3C=N); 3.05 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.10 (2H, s, CH_2Ph); 5.35 (1H, s, H-6); 6.96 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.15-7.34 (2.8H, m, $=CHNMe_2$ 2*E*-isomer, H-5, H-6 C_6H_4); 7.44 (1H, d, $^3J = 7.3$, H-4 C_6H_4); 7.48 (2H, br. s, =CHC(Me)=N, H-2 C_6H_4). Mass spectrum, *m/z*: 603 [M+Na^+].

***tert*-Butyl Ester of 7*Z*-[2-*anti*-(4-Bromobenzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylamino-methylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-11d) and *tert*-Butyl Ester of 7*Z*-[2-*syn*-(4-Bromobenzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*syn*-11d)** was obtained from a mixture of the *anti* and *syn* isomers of the *tert*-butyl ester of 7*Z*-[2-(4-bromobenzyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.43 (2:1 ethyl acetate–hexane) gave 47 mg (43%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *anti*-**11d**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.13 (3H, s, CH_3); 2.23 (3H, s, CH_3C=N); 3.04 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.16 (2H, s, CH_2Ph); 5.41 (1H, s, H-6); 6.83 (1H, s, =CHC(Me)=N); 6.93 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.23 (0.8H, s, $=CHNMe_2$ 2*E*-isomer); 7.23 (2H, d, $^3J = 8.3$, H-2, H-6 C_6H_4); 7.48 (2H, d, $^3J = 8.3$, H-3, H-5 C_6H_4). Mass spectrum: 602/604 [M+Na^+].

The fractions with R_f 0.37 (2:1 ethyl acetate–hexane) gave 32 mg (29%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *syn*-**11d**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.20 (3H, s, CH_3); 2.22 (3H, s, CH_3C=N); 3.05 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.33 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.09 (2H, s, CH_2Ph); 5.33 (1H, s, H-6); 6.95 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.17-7.25 (2.8H, m, $=CHNMe_2$ 2*E*-isomer); H-2, H-6 C_6H_4); 7.46 (1H, br. s, =CHC(Me)=N); 7.48 (2H, d, $^3J = 8.3$, H-3, H-5 C_6H_4). Mass spectrum, *m/z*: 602/604 [M+Na^+].

***tert*-Butyl Ester of 2(*E/Z*)-(N,N-Dimethylaminomethylene)-3-methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-chloro-benzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*anti*-11e) and *tert*-Butyl Ester of 2(*E/Z*)-(N,N-Dimethylaminomethylen-7*Z*-[2-*syn*-(2-chlorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-11e)** were obtained from a mixture of the *anti* and *syn* isomers of the *tert*-butyl ester of 3-methyl-1,1-dioxo-7*Z*-(2-(2-chlorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic acid.

The fractions with R_f 0.30 (1:1 ethyl acetate–hexane) gave 22 mg (36%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *anti*-**11e**; mp 134-136°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.17 (3H, s, CH_3); 2.23 (3H, s, CH_3C=N); 3.04 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.34 (2H, s, CH_2Ph); 5.42 (1H, br. s, H-6); 6.84 (1H, br. s, =CHC(Me)=N); 6.93 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.20-7.43 (4.8H, m, $=CHNMe_2$ 2*E*-isomer, C_6H_4). Mass spectrum, *m/z*: 558/560 [M+Na$^+$].

The fractions with R_f 0.21 (1:1 ethyl acetate–hexane) gave 31 mg (51%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *syn*-**11e**; mp 130-132°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.23 (6H, br. s, CH_3, CH_3C=N); 3.05 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.33 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.28 (2H, s, CH_2Ph); 5.36 (1H, s, H-6); 6.96 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 7.20-7.44 (4.8H, m, $=CHNMe_2$ 2*E*-isomer, C_6H_4); 7.54 (1H, br. s, =CHC(Me)=N). Mass spectrum, *m/z*: 558/560 [M+Na$^+$].

***tert*-Butyl Ester of 2(*E/Z*)-(N,N-Dimethylaminomethylene)-3-methyl-1,1-dioxo-7*Z*-[2-*anti*-(2-fluorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*anti*-11f) and *tert*-Butyl Ester of 2(*E/Z*)-(N,N-Dimethylaminomethylene)-3-methyl-1,1-dioxo-7*Z*-[2-syn-(2-fluorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic Acid (*syn*-11f)** were obtained from a mixture of the *anti* and *syn* isomers of the *tert*-butyl ester of 3-methyl-1,1-dioxo-7*Z*-[2-(2-fluorobenzyloxyimino)propylidene]-3-cephem-4-carboxylic acid.

The fractions with R_f 0.29 (1:1 ethyl acetate–hexane) gave 8 mg (35.5%) of a 4:1 mixture of the 2*E*- and 2*Z*-isomers of *anti*-**11f**; mp 85-87°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.13 (3H, s, CH_3); 2.23 (3H, s, CH_3C=N); 3.04 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.29 (2H, s, CH_2Ph); 5.42 (1H, br. s, H-6); 6.84 (1H, br. s, =CHC(Me)=N); 6.93 (0.2H, s, $=CHNMe_2$ 2*Z* isomer); 6.97-7.19 (2H, m, H-4, H-5 C_6H_4); 7.23 (0.8H, s, $=CHNMe_2$ 2*E*-isomer); 7.27-7.45 (2H, m, H-3, H-6 C_6H_4). Mass spectra, *m/z*: 520 [M]$^+$.

The fractions with R_f 0.20 (1:1 ethyl acetate–hexane) gave 10 mg (45.6%) of a 4:1 mixture of the 2*E*-and 2*Z*-isomers of *syn*-**11f**; mp 81-83°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.53 (9H, s, C_4H_9); 2.21 (3H, s, CH_3); 2.22 (3H, s, CH_3C=N); 3.04 (4.8H, s, $N(CH_3)_2$ 2*E*-isomer); 3.32 (1.2H, s, $N(CH_3)_2$ 2*Z*-isomer); 5.22 (2H, s, CH_2Ph); 5.34 (1H, br. s, H-6); 6.95 (0.2H, s, $=CHNMe_2$ 2*Z*-isomer); 6.98-7.19 (2H, m, H-4, H-5 C_6H_4); 7.24 (0.8H, s, $=CHNMe_2$ 2*E*-isomer); 7.27-7.44 (2H, m, H-3, H-6 C_6H_4); 7.49 (1H, br. s, =CHC(Me)=N). Mass spectrum, *m/z*: 520 [M]$^+$.

3*Z*-[2-anti-(Arylmethoxyimino)propylidene]-1-*tert*-butoxycarbonylmethyl-4-(5-methyl-4-isoxazolylsulfonyl)azetidin-2-ones (*anti*-14a,b,d). Typical procedure. Hydroxylamine hydrochloride (22 mg, 0.319 mmol) was added to a solution of a mixture of the *syn* and *anti* isomers of *tert*-butyl ester of 7*Z*-[2-(arylmethoxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (80 mg, 0.159 mmol) in acetonitrile (25 ml). The reaction mixture was stirred for 2 h at 40-50°C and evaporated at reduced pressure. The residue was fractionated on a silica gel with ethyl acetate–hexane as the eluent (the solvent ratio was varied from 1:5 to 1:2) to give azetidinones **14a, 14b,** and **14d**.

3Z-[2-anti-(2-Benzyloxyimino)propylidene]-1-*tert*-butoxycarbonylmethyl-4-(5-methyl-4-isoxazolylsulfonyl)azetidine-2-one (*anti*-14a) was obtained from a mixture of the *syn* and *anti* isomers of the *tert*-butyl ester of 7Z-[2-(benzyloxyimino)propylidene]-2(*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.33 (1:1 ethyl acetate–hexane) gave *anti*-**14a** in 64% yield; mp 76-78°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, C_4H_9); 2.15 (3H, s, CH_3C=N); 2.50 (3H, s, CH_3 isoxazole); 4.05, 4.40 (2H, two d, AB system, ^2J = 18, NCH_2CO_2); 5.25 (2H, s, CH_2Ph); 5.75 (1H, s, H-4); 6.65 (1H, s, =CH(Me)=N); 7.30-7.44 (5H, m, C_6H_5); 8.17 (1H, s, H-3 isoxazole). Mass spectrum, *m/z*: 512 [M+Na$^+$].

3*Z*-[2-*anti*-(2-Bromobenzyloxyimino)propylidene]-1-*tert*-butoxycarbonylmethyl-4-(5-methyl-4-isoxazolesulfonyl)azetidin-2-one (*anti*-14b) was obtained from a mixture of the *syn* and *anti* isomers of the *tert*-butyl ester of 7*Z*-[2-(2-bromobenzyloxyimino)propylidene]-(2*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.43 gave an oily product in 15% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, C_4H_9); 2.19 (3H, s, CH_3C=N); 2.54 (3H, s, CH_3 isoxazole); 4.05, 4.41 (2H, two d, AB system, ^2J = 18, NCH_2CO_2); 5.34 (2H, s, CH_2Ph); 5.77 (1H, s, H-4); 6.65 (1H, s, =CHC(Me)=N); 7.12-7.38 (3H, m, H-4, H-5, H-6 C_6H_4); 7.58 (1H, d, ^3J = 7.4, H-3 C_6H_4); 8.21 (1H, s, H-3 isoxazole). Mass spectrum, *m/z*: 590 [M+Na$^+$].

3*Z*-[2-*anti*-(4-Bromobenzyloxyimino)propylidene]-1-tert-butoxycarbonylmethyl-4-(5-methyl-4-isoxazolesulfonyl)azetidin-2-one (*anti*-14d) was obtained from a mixture of the *syn* and *anti* isomers of the *tert*-butyl ester of 7*Z*-[2-(4-bromobenzyloxyimino)propylidene]-(2*E/Z*)-(N,N-dimethylaminomethylene)-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid.

The fractions with R_f 0.39 gave an oily product in 8% yield. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, C_4H_9); 2.14 (3H, s, CH_3C=N); 2.52 (3H, s, CH_3 isoxazole); 4.05, 4.40 (2H, two d, AB system, ^2J = 18, NCH_2CO_2); 5.19 (2H, s, CH_2Ph); 5.75 (1H, s, H-4); 6.62 (1H, s, =CHC(Me)=N); 7.24 (2H, d, ^3J = 8.4, H-2, H-6 C_6H_4); 7.50 (2H, d, ^3J = 8.4, H-3, H-5 C_6H_4); 8.18 (1H, s, H-3 isoxazole). Mass spectrum, *m/z*: 590 [M+Na$^+$].

***tert*-Butyl Ester of 7*Z*-[2-*anti*-(4-Bromophenylhydrazono)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-15).** 4-Bromophenylhydrazine hydrochloride (85 mg, 0.381 mmol) and sodium acetate (32 mg, 0.381 mmol) were added to a solution of *tert*-butyl ester 7*Z*-acetylmethylene-3-methyl-1,1-dioxo-cephem-4-carboxylic acid (100 mg, 0.293 mmol) in methanol (10 ml). The reaction mixture was stirred for 24 h at room temperature and then evaporated at reduced pressure. The residue was fractionated on a silica gel column. The fractions with R_f 0.23 (1:1 ethyl acetate–hexane) gave cephem *anti*-**15** in 68% yield; mp 210-213°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48 (9H, s, C_4H_9); 1.91 (3H, s, CH_3); 2.12 (3H, s, CH_3C=N); 4.16, 4.34 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 6.25 (1H, s, H-6); 6.97 (1H, s, =CHC(Me)=N); 7.24 (2H, d, ^3J = 8.8, H-2, H-6 C_6H_4); 7.43 (2H, d, ^3J = 8.8, H-3, H-5 C_6H_4); 10.15 (1H, s, NH). Mass spectrum, *m/z*: 534 [M+Na$^+$].

***tert*-Butyl Ester of 7*Z*-[2-*anti*-(2-Bromobenzoyloxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic Acid (*anti*-16).** 2-Bromobenzoic acid chloride (36 mg, 0.168 mmol) and pyridine (4 mg, 0.056 mmol) were added to a solution of *tert*-butyl ester of a mixture of *syn* and *anti* isomers of *Z*-[2-(hydroxyimino)propylidene]-3-methyl-1,1-dioxo-3-cephem-4-carboxylic acid (20 mg, 0.056 mmol) in 10 ml acetonitrile. The reaction mixture was stirred for 72 h at room temperature, diluted with 100 ml 5% aqueous NaCl, and extracted with two 30-ml portions of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated at reduced pressure. The residue was fractionated on a silica gel column. The fractions with R_f 0.57 (1:1 ethyl acetate–hexane) gave cephem *anti*-**16** in 54% yield; mp 128-132°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.54 (9H, s, C_4H_9); 2.10 (3H, s, CH_3); 2.35 (3H, s, CH_3C=N); 3.65, 3.93 (2H, two d, AB system, ^2J = 17.6, SO_2CH_2); 5.58 (1H, s, H-6); 7.09 (1H, s, =CHC(Me)=N); 7.34-7.48 (2H, m, H-4, H-5 C_6H_4); 7.66-7.75 (1H, m, H-3 C_6H_4); 7.77-7.86 (1H, m, H-6 C_6H_4). Mass spectrum, *m/z*: 561/563 [M+Na$^+$].

Determination of Cytotoxic Activity *in vitro*. The cytotoxic properties of the products relative to monolayer malignant and normal cells at $c = (2\text{-}5)\cdot10^4$ cells/ml: HT-1080 (human fibrosarcoma); MG-22A (murine hepatoma); 3T3 (embryonal murine fibroblasts) were determined in 96-well panels using CV, MTT, and NR dyes according to a standard procedure [5].

Cellular Generation of NO Radicals. The determination of the nitric oxide radicals in acid media according to Gracey [6] was carried out in plastic 96-well panels. The NO radical concentration (in nmoles) in the culture medium with the surviving cells after incubation for 72 h in the presence of the test compound at c = 50 μg/ml in the 200-μl well was used to calculate the specific NO generating activity of the compounds (TG_{100}):

$$TG_{100} = G\ 100/C\ (\text{nmol}/\mu\text{l});$$

Where G is the NO concentration (nmoles) in 200-μl culture medium, *C* is the percentage of surviving cells determined by their coloration with CV.

This work has been partly supported by the European Social Fund within the National Programme "Support for the carrying out doctoral study programm's and post-poctoral researches" project "Support for the development of doctoral Studies at Riga Technical University".

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