Chemistry of Heterocyclic Compounds, Vol. 41, No. 5, 2005

BROMINATION OF *tert*-BUTYL ESTERS OF 7α-CHLORO AND 7-ALKYLIDENEDEACETOXY-CEPHALOSPORANIC ACID SULFONES

M. Vorona, G. Veinberg, I. Turovskis, and E. Lukevics

The action of N-bromosuccinimide on tert-butyl esters of 7α-chloro- and 7-alkylidenedeacetoxycephalosporanic acid sulfones upon irradiation with visible light leads to the formation of a mixture of the product of allylic bromination of the 3-methyl group, namely, 3-bromomethyldeacetoxycephalosporanate, and the product of replacement of a proton at $C_{(2)}$ in the latter, namely, 2-bromo-3-bromomethyldeacetoxycephalosporanate. Small amounts of E-isomers were also obtained in the case of the Z-isomer of the 7-(4-nitrobenzylidene) derivative. In the case of the 7α-chloro derivative only substitution of one or two protons at $C_{(2)}$ occurs during bromination without irradiation, the same as the isomerization of the double bond in the cepheme system.

Keywords: N-bromosuccinimide, *tert*-butyl esters of substituted deacetoxycephalosporanic acid sulfones, allylic bromination.

The allylic bromination of deacetoxycephalosporin is an efficient method for the structural modification of its 3-methyl group in the synthesis of antibiotic analogs with improved antibacterial properties and obtaining precursors of compounds with antibacterial and anticancer activity released by enzymatic hydrolysis of the β-lactam ring [1-3]. Recent research has concerned the inhibitory properties of some cephalosporin sulfone esters synthesized by analogous modification of the methyl group relative to serine proteases [4-6].

The allylic bromination of the *tert*-butyl ester of 7α-chlorodeacetoxycephalosporanic acid sulfone (**1**) by N-bromosuccinimide (NBS) was carried out in CCl_4 at reflux in the presence of azodiisobutyronitrile (AIBN) over 5 h [4].

In the present work, the reaction of **1** with NBS was carried out using external irradiation of the flask containing the reagent mixture in benzene at reflux using a 250-500-W incandescent lamp or by irradiation of a solution of the reagents in methylene chloride at room temperature using an immersed 12-W halogen lamp.

In both cases, thin-layer chromatographic analysis of the reaction solution showed the starting ester **1**, which disappeared in 20-20 min, as well as the desired product **2** and an unstable, less polar product, which disappeared after adding triphenylphosphine. The previously described formation of the trimethylsilyl ester of the sulfoxide of 3-methyl-7α-phenylacetamidocephalosporanic acid and its 2-bromo-3-bromomethyl derivative by allylic bromination and the debromination of the latter derivative at $C_{(2)}$ [7] suggest that the unstable product is the 2-bromo-3-bromomethylcephalosporanate ester **3** (see Scheme 1).

* Dedicated to Academician N. K. Kochetkov on the occasion of this ninetieth birthday.

Latvian Institute of Organic Synthesis, LV-1006 Riga, Latvia; e-mail: vorona@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 767-774, May, 2005. Original article submitted February 15, 2003, submitted after revision March 10, 2004.

The reaction of ester **1** with NBS in benzene at room temperature without irradiation or catalyst is complete after 2 h. The replacement of benzene by dichloromethane reduces the reaction rate. The reaction is complete in only a few minutes when lutidine is added. The reaction yields products of the bromination of the cephalosporin system at $C_{(2)}$ **4-6**, which are converted to starting compound **1** upon the addition of PPh_3. The separation of the reaction mixture by column chromatography using 1:2 ethyl acetate–hexane as the eluent gave two fractions. The less polar fraction with R_f 0.71 contained a 3:7 mixture of esters **4** and **5** as indicated by ^{1}H NMR spectroscopy and HPLC, while the more polar fraction with R_f 0.66 was a 4:6 mixture of esters **5** and **6**. HPLC analysis indicated that use of Br_2 instead of NBS leads to the formation of a 3:7 mixture of **4** and **5**, which could not be resolved.

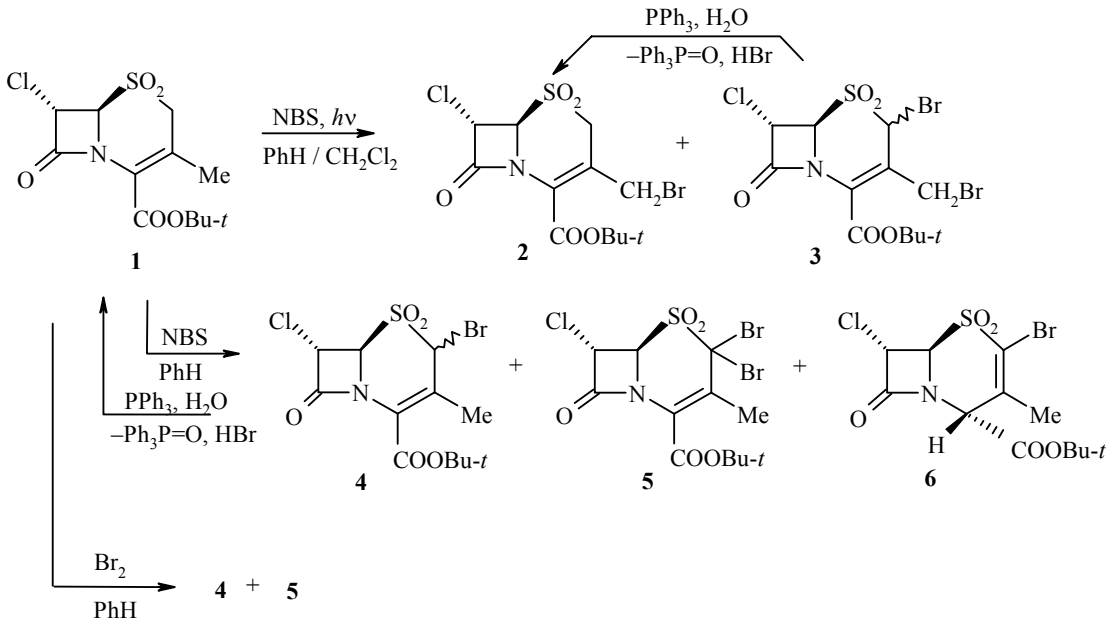
^{1}H NMR spectral analysis of the fractions with R_f 0.71 and 0.66 showed that products **4-6** differ only in the substitution of the protons at $C_{(2)}$ and position of the double bond in the cepheme system. Comparison of the signals of the methine protons with the literature values for analogous signals of structurally similar cephalosporin analogs and the ratio of the integral intensities and percentage composition of the products in each fraction permitted identification of isomeric monobromides **4** and **6** and dibromide **5**.

Allylic bromination of the *Z*-isomers of alkylidenecephalosporanate sulfones **7a** and **7b** gave the desired *Z*-isomers of 3-bromomethylcephalosporanates **8a** and **8b** as well as the *Z*-isomers of dibromides **9a** and **9b**, which are readily converted to *Z*-monobromides **8a** and **8b** upon treatment with triphenylphosphine (Scheme 2). Dibromides *Z*-**9a** and *Z*-**9b**, in contrast to their 7α-chloro analogs **3**, proved stable, which permitted their isolation and characterization.

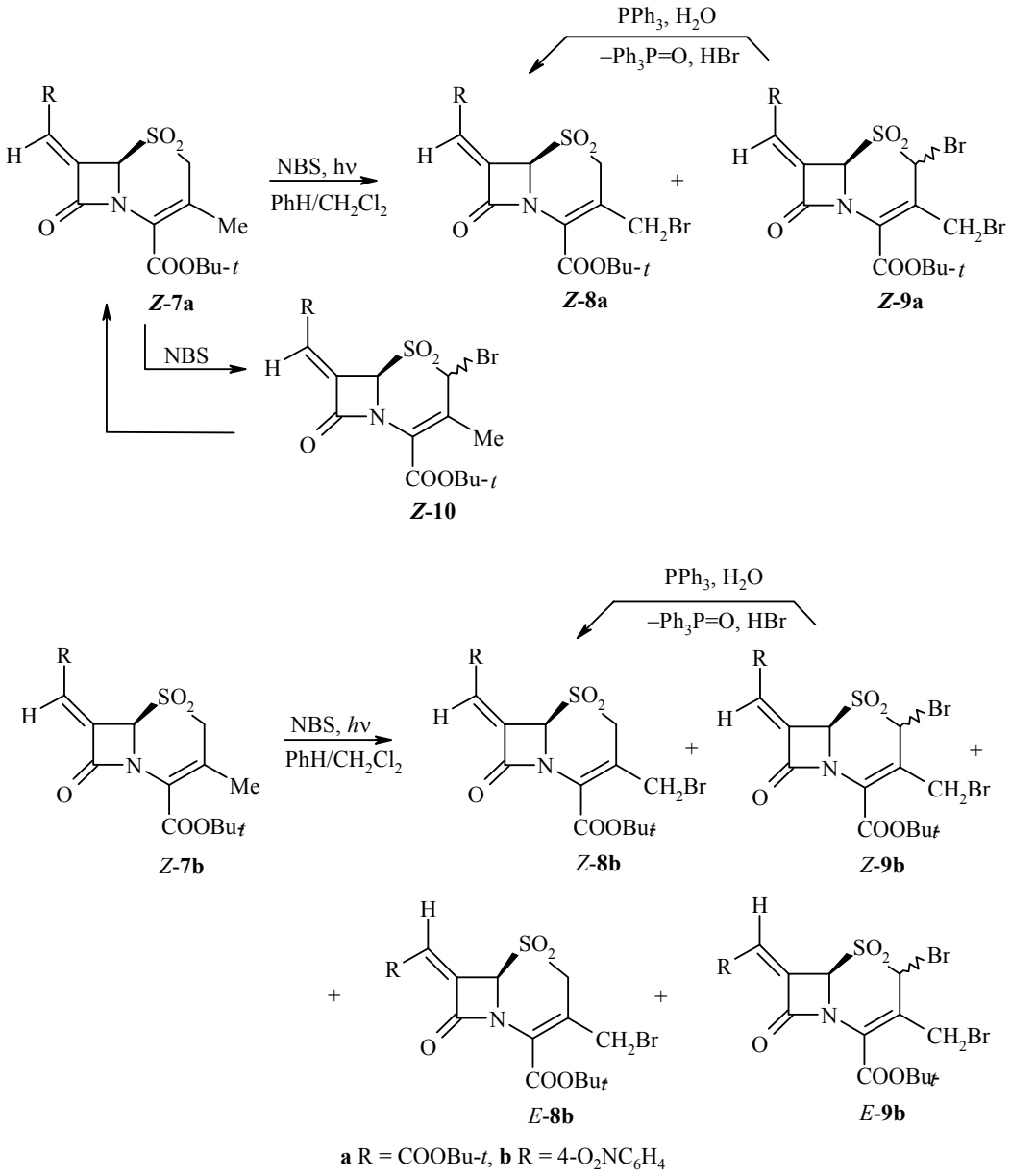
In the case of *Z*-**7b** with a 7-*Z*-4-nitrobenzylidene side chain, we isolated the *Z*-isomers of monobromide **8b** and dibromide **9b** as well as small amounts of *E*-isomers of **8b** and **9b**, which is in accord with the ability of the starting ester *Z*-**7b** to convert to a 43:57 mixture of the *Z*- and *E*-isomers upon brief irradiation with a halogen lamp.

The reaction of ester *Z*-**7a** with NBS without irradiation proceeded through an ionic mechanism to give 2-bromocephalosporanate *Z*-**10**, which converts to starting ester *Z*-**7a** upon debromination using triphenylphosphine.

Scheme 1



Scheme 2



a R = COOBu-*t*, **b** R = 4-$O_2NC_6H_4$

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WH-90/DS spectrometer for $CDCl_3$ solutions at 90 MHz using TMS as the internal standard. The elemental analysis was carried out on a Carlo Erba 1108 analyzer. The reaction course was monitored by thin-layer chromatography on Merck Keiselgel plates with UV detection. The HPLC data were obtained on a Dupont Model 8800 chromatograph equipped with a UV detector (λ = 254 nm) and 4.6×250-mm column packed with Ultrasphere Si using 1:3 ethyl acetate–hexane as the eluent. The flow rate was 0.8 1.5 ml/min. Preparative column chromatography was carried out on Merck Kieselgel silica gel (0.063-0.230 mm). Acros and Aldrich reagents were used. The bromination was carried out in absolute benzene subjected to prior treatment with concentrated sulfuric acid or methylene chloride.

Ester **1** was prepared according to Alpegiani et al. [4].

***Z*-Isomers of *tert*-Butyl Ester of 7-Alkylidenecephalosporanic Acid Sulfones (*Z*-7a and *Z*-7b)** were prepared according to our previous procedure [10]. An alkylidenetriphenylphosphorane was added to a solution of 5 mmoles *tert*-butyl ester of 7-oxodeacetoxycephalosporanic acid (**11**) [9] in 20 ml dichloromethane and the mixture was stirred at room temperature for 40 min. The solvent was then evaporated at reduced pressure and the residue was purified on a chromatographic column using 1:1 ethyl acetate–hexane as the eluent. The resultant mixture of isomeric *tert*-butyl esters of 7-alkylidenedeacetoxycephalosporanates was oxidized with 3-chloroperbenzoic acid (12 mmol) in dichloromethane (20 ml) over 2 h at room temperature. The reaction mixture was washed with 5% aqueous sodium carbonate and, then, water. The organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated off at reduced pressure. Column chromatography using 1:1 ethyl acetate–hexane as the eluent gave ester *Z*-**7**.

***Z*-Isomer of *tert*-Butyl Ester of 7-(*tert*-Butoxycarbonylmethylene)diacetoxycephalosporanic Acid Sulfone (*Z*-7a)** was obtained from *tert*-butoxycarbonylmethylenetriphenylphosphorane in 28% yield (relative to starting ester **11**), R_f 0.43 (1:1 ethyl acetate–hexane); mp 65-67°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.53 (18H, s, $2C_4H_9$); 2.15 (3H, s, CH_3); 3.64 (2H, AB system, *J* = 18.0, SCH_2); 5.51 (1H, br. s, 6-H); 6.51 (1H, d, *J* = 1.0, –CH=). Found, %: C 54.42; H 6.49; N 3.63. $C_{18}H_{25}NO_7S$. Calculated, %: C 54.12; H 6.31; N 3.51.

***Z*-Isomer of *tert*-Butyl Ester of 7-(4-Nitrobenzylidene)deacetoxycephalosporanic Acid Sulfone (*Z*-7b)** was obtained from (4-nitrobenzylidene)triphenylphosphorane in 21% yield (relative to ester **11**), R_f 0.34 (1:1 ethyl acetate–hexane); mp 115-116°C (ethyl acetate). Content of ester *Z*-**7b** 97% (HPLC data). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.55 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 3.71, 4.06 (2H, AB system, *J* = 18.0, SCH_2); 5.57 (1H, br. s, 6-H); 7.42 (1H, br. s, –CH=); 7.93 and 8.28 (2H, d, *J* = 8.0, C_6H_4).

Allylic Bromination of *tert*-Butyl Esters of 7α-Chloro- (1) and *Z*-7-Alkylidene-deacetoxycephalosporanic Acid Sulfones (7a, 7b) (General Procedure). A. A mixture of ester **1**, *Z*-**7a** or *Z*-**7b** (1.0 mmol), and NBS (1.1 mmol) in benzene (50 ml) heated at reflux was irradiated with a 100-W incandescent lamp for 30 min until completion of the reaction as indicated by thin-layer chromatography. The solvent was then evaporated. Product **2** was isolated from the residue by column chromatography with 1:2 ethyl acetate–hexane as the eluent (in the case of starting ester **1**). Products *Z*-**8a** and *Z*-**9a** were obtained from starting ester *Z*-**7a**. Products *Z*-**8b**, *Z*-**9b**, *E*-**8b**, and *E*-**9b** were obtained from starting ester *Z*-**7b** [7].

B. A mixture of ester **1** (1 mmol) and NBS (1.1 mmol) in absolute methylene chloride (50 ml) was irradiated with a 12-W halogen lamp immersed directly in the solvent at room temperature until completion of the reaction as indicated by thin-layer chromatography (~30 min). The reaction mixture was then worked up and the products were isolated as in procedure A.

***tert*-Butyl Ester of 3-Bromomethyl-7α-chlorodeacetoxycephalosporanic Acid Sulfone (2)** was obtained in 40% yield according to procedure A and 53% yield according to procedure B; mp 139-141°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.58 (9H, s, C_4H_9); 3.82 and 4.22 (2H, AB system, *J* = 18.0, SCH_2); 4.17 and 4.51 (2H, AB system, *J* = 10.0, CH_2Br); 4.82 (1H, br. s, H-6); 5.24 (1H, br. s, H-7). Found, %: C 35.57; H 3.75; N 3.29. $C_{12}H_{15}BrClNO_5S$. Calculated, %: C 35.97; H 3.77; N 3.50.

***tert*-Butyl Ester of *Z*-3-Bromomethyl-7-(*tert*-butoxycarbonylmethylene)deacetoxycephalosporanic Acid Sulfone (*Z*-8a)** was obtained in 67% yield according to procedure A and 71% yield according to procedure B, R_f 0.37 (1:3 ethyl acetate–hexane); mp 146-147°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.55 (18H, s, $2C_4H_9$); 3.77 and 4.20 (2H, AB system, *J* = 18.0, SCH_2); 4.24, 4.58 (2H, AB system, *J* = 10.0, CH_2Br); 5.69 (1H, d, *J* = 1.0, H-6); 6.57 (1H, d, *J* = 1.0, –CH=). Found, %: C 45.29; H 5.11; N 3.05. $C_{18}H_{24}BrNO_7S$. Calculated, %: C 45.20; H 5.06; N 2.93.

***tert*-Butyl Ester of *Z*-3-Bromomethyl-7-(4-nitrobenzylidene)deacetoxycephalosporanic Acid Sulfone (*Z*-8b)** was obtained from ester *Z*-**7b** in 43% yield according to procedure A and 56% yield according to procedure B, R_f 0.17 (1:2 ethyl acetate–hexane); mp 139-141°C. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.57

(9H, s, C_4H_9); 3.86, 4.31 (2H, AB system, J = 18.0, SCH_2); 4.20, 4.57 (2H, AB system, J = 10.0, CH_2Br); 5.66 (1H, br. s, H-6); 7.49 (1H, br. s, –CH=); 7.84, 8.29 (2H, d, and 2H, d, J = 9.0, C_6H_4). Found, %: C 45.94; H 4.15; N 5.49. $C_{19}H_{19}BrN_2O_7S$. Calculated, %: C 45.70; H 3.84; N 5.61.

***tert*-Butyl Ester of *E*-3-Bromomethyl-7-(4-nitrobenzylidene)deacetoxycephalosporanic Acid Sulfone (*E*-8b)** was obtained in 6% yield according to procedure A, R_f 0.17 (1:2 ethyl acetate–hexane); mp 105-107°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.64 (9H, s, C_4H_9); 3.82, 4.28 (2H, AB system, J = 17.0, SCH_2); 4.20, 4.57 (2H, AB system, J = 10.0, CH_2Br); 5.31 (1H, br. s, H-6); 7.00 (1H, br. s, –CH=); 8.13, 8.33 (2H, d, and 2H, d, J = 10.0, C_6H_4). Found, %: C 45.98; H 4.10; N 5.33. $C_{19}H_{19}BrN_2O_7S$. Calculated, %: C 45.70; H 3.84; N 5.61.

***tert*-Butyl Ester of *Z*-2-Bromo-3-bromomethyl-7-*tert*-butoxycarbonylmethylenedeacetoxycephalosporanic Acid Sulfone (*Z*-9a)** was obtained in 6% yield according to procedure A, R_f 0.17 (1:3 ethyl acetate–hexane); mp 124-126°C (ethyl acetate). ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.55 (18H, s, $2C_4H_9$); 4.11, 4.57 (2H, AB system, J = 10.0, CH_2Br); 4.95 (1H, s, 2-H); 6.22 (1H, d, J = 1.0, H-6); 6.64 (1H, d, J = 1.0, –CH=). Found, %: C 39.12; H 4.30; N 2.61%. $C_{18}H_{23}Br_2NO_7S$. Calculated, %: C 38.80; H 4.16; N 2.51.

***tert*-Butyl Ester of *Z*-2-Bromo-3-bromomethyl-7-(4-nitrobenzylidene)deacetoxycephalosporanic Acid Sulfone (*Z*-9b)** was obtained in 1.5% yield according to procedure A, R_f 0.54 (1:2 ethyl acetate–hexane); mp 82-85°C (ethyl acetate). The content of ester *Z*-**9b** was >93% (HPLC data). ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.62 (9H, s, C_4H_9); 4.15, 4.58 (2H, AB system, J = 10.0, CH_2Br); 5.62 (1H, s, 2-H); 6.26 (1H, d, J = 1.0, 6-H); 7.58 (1H, br. s, –CH=); 7.86, 8.33 (2H, d, and 2H, d, J = 9.0, C_6H_4).

***tert*-Butyl Ester of *E*-2-Bromo-3-bromomethyl-7-(4-nitrobenzylidene)deacetoxycephalosporanic Acid Sulfone (*E*-9b)** was obtained in 1% yield according to procedure A as an amorphous substance, R_f 0.46 (1:2 ethyl acetate–hexane). The content of ester *E*-**9b** was >94% (HPLC data). ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.62 (9H, s, C_4H_9); 4.13, 4.53 (2H, AB system, J = 11.0, CH_2Br); 5.57 (1H, s, 2-H); 5.93 (1H, d, J = 0.5, 6-H); 7.07 (1H, d, J = 0.5, –CH=); 8.13, 8.31 (2H, d, J = 10.0 and 2H, d, J = 10.0, C_6H_4).

Ionic Bromination of Esters 1 and *Z*-7a. A mixture of ester **1** (100 mg, 0.30 mmol) and NBS (66 mg, 0.37 mmol) in absolute benzene (10 ml) was stirred in the dark at room temperature for 2 h. The solvent was evaporated. The residue was subjected to column chromatography using 1:3 ethyl acetate–hexane as the eluent to give 23 mg of a 3:7 mixture of **4** and **5** (as indicated by HPLC), R_f 0.71 (1:3 ethyl acetate–hexane) and 25 mg of a 4:6 mixture of **4** and **6**, R_f 0.66 (1:3 ethyl acetate–hexane). The total yield of these products in the mixtures was >97% (HPLC data).

When Br_2 (0.30 mmol) was used instead of NBS, a 3:7 mixture of **4** and **5** was obtained, R_f 0.71 (1:3 ethyl acetate–hexane).

***tert*-Butyl Ester of 2-Bromo-7α-chlorodeacetoxycephalosporanic Acid Sulfone (4).** ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.55 (9H, s, C_4H_9); 2.28 (3H, s, CH_3); 4.95 (1H, s, 2-H); 5.37 (1H, d, J = 0.5, 7-H).

***tert*-Butyl Ester of 2,2-Dibromo-7α-chlorodeacetoxycephalosporanic Acid Sulfone (5).** ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.51 (9H, s, C_4H_9); 2.13 (3H, s, CH_3); 4.82 (1H, d, J = 0.5, 6-H); 5.49 (1H, d, J = 0.5, 7-H).

***tert*-Butyl Ester of 2-Bromo-7α-chloro-3-methylceph-2-eme-4-carboxylic Acid Sulfone (6).** ^{1}H NMR spectrum, δ, ppm, (J, Hz): 1.55 (9H, s, C_4H_9); 2.08 (3H, s, CH_3); 4.66 (1H, d, J = 0.5, 6-H); 5.42 (1H, d, J = 0.5, 7-H); 6.28 (1H, s, 4-H).

***tert*-Butyl Ester of *Z*-2-Bromo-7α-*tert*-butoxycarbonylmethylenedeacetoxycephalosporanic Acid Sulfone (10)** was obtained under the bromination conditions described above from ester *Z*-**7a** (25 mg, 0.1 mmol) and NBS (18.4 mg, 0.1 mmol) in absolute benzene (3 ml) over 30 min. The reaction yielded 10 mg of an oily substance containing >97% ester **10** (HPLC data). Yield 20%, R_f 0.60 (1:1 ethyl acetate–hexane). ^{1}H NMR spectrum, δ, ppm: 1.55 (18H, s, $2C_4H_9$); 2.17 (3H, s, CH_3); 5.00 (1H, s, 2-H); 6.20 (1H, br. s, 6-H); 6.62 (1H, br. s, –CH=). Found, %: C 45.42; H 5.21; N 3.11. $C_{18}H_{24}BrNO_7S$. Calculated, %: C 45.20; H 5.06; N 2.93.

REFERENCES

1. B. R. Cowley, D. C. Humber, B. Laundon, and A. G. Long, *Tetrahedron*, **39**, 337 (1983).
2. M. Botta, F. De Angelis, A. Gambacorta, F. Giannessi, and R. Nicoletti, *Gazz. Chim. Ital.*, **115**, 169 (1985).
3. L. N. Jungheim and T. A. Shepherd, *Chem. Rev.*, **94**, 1553 (1994).
4. M. Alpegiani, A. Baici, P. Bissolino, P. Carminati, G. Cassinelli, S. Del Nero, G. Franceschi, P. Orezzi, E. Perrone, V. Rizzo,and N. Sacchi, *Eur. J. Med. Chem.*, **27**, 875 (1992).
5. M. Alpegiani, P. Bissolino, R. Corigli, S. Del Nero, E. Perrone, V. Rizzo, N. Sacchi, G. Cassinelli, and G. Franceschi, *J. Med. Chem.*, **37**, 4003 (1994).
6. G. Veinberg, I. Shestakova, L. Petrulanis, N. Grigan, D. Musel, D. Zeile, I. Kanepe, I. Domrachova, I. Kalvinsh, A. Strakovs, and E. Lukevics, *Bioorg. Med. Chem. Lett.*, **7** 843 (1997).
7. J. Verweij and E. de Vroom, *Rec. Trav. Chim. Pays-Bas*, **112**, 66 (1993).
8. G. Veinberg, I. Shestakova, N. Grigan, D. Musel, I. Kanepe, I. Domrachova, V. Grigoryeva, O. Zharkova, I. Turovskis, I. Kalvinsh, A. Strakovs, and E. Lukevics, *Eur. J. Med. Chem.*, **33**, 755 (1998).
9. J. D. Buynak, A. Srnivasa Rao, and S. D. Nidamarthy, *Tetrahedron Lett.*, **39**, 4945 (1998).
10. G. Veinberg, M. Vorona, I. Shestakova, I. Kanepe, O. Zharkova, R. Mezapuke, I. Turovskis, I. Kalvinsh, and E. Lukevics, *Bioorg. Med. Chem.*, **8**, 1033 (2000).