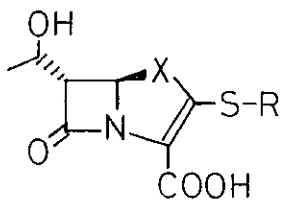
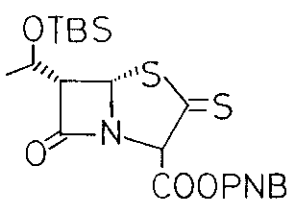
SYNTHETIC STUDIES OF 1-AZAPENEM

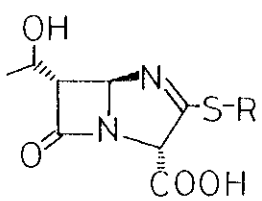
Tomoyuki Shibata, Yukio Sugimura,* Sadao Sato,[+] and Kayoko Kawazoe[+]
Chemical Research Laboratories, and Analytical and Metabolic Research Laboratories,[+] Sankyo Co., Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo, 140, Japan

Abstract- Total synthesis of 1-azapenem (5) is reported. The key intermediate 24 was synthesized by the intramolecular cyclization of 17 and subsequent desilylation. Alkylation of 24 and subsequent hydrogenolysis gave 5.

Since the synthesis of penems by Woodward [1] and the discovery of thienamycin by a Merck group,[2] the interest of chemists has been focused on the chemistry of penems and carbapenems because of their strong antibacterial activities and their unique chemical structures.[3] Our interest in penem and carbapenem synthesis led to the development of a new method for the synthesis of 2-thiopenem (1) and the synthesis of 2-thioxopenam (2), an important synthetic intermediate for further transformation to 2-thio-substituted penem derivatives,[4] and the synthesis of RS-533 (3), a carbapenem derivative with apparent great antibacterial potential.[5] In fact, we have synthesized numerous penem and carbapenem derivatives and demonstrated that the 1-hydroxyethyl substituent is necessary for penems and carbapenems to display good antibacterial activity.





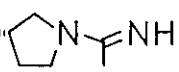


1 X; S

2

5

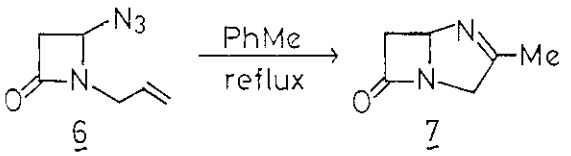
3 X; CH_2, R;



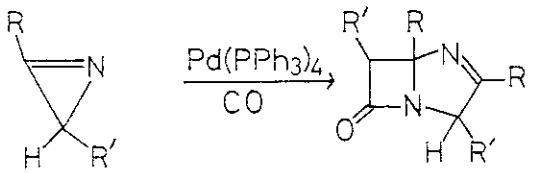
TBS = $-\overset{|}{\underset{|}{Si}}-$

4 X;

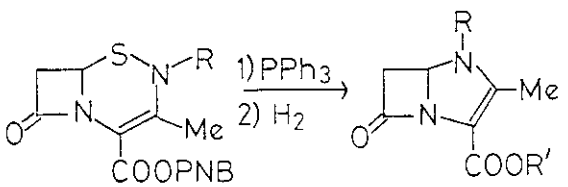
Currently we have directed our interests to the 1-azapenem compound (4), which is substituted by a nitrogen atom at the 1-position of the penem. However reports of azapenem synthesis are few. Nagakura[6] obtained 7 by refluxing 6 in toluene. Alper *et al.*[7] obtained 9 by treatment of 8 with palladium catalyst in the presence of carbon monoxide. These synthesized compounds were racemic and devoid of the essential substituents. Ross *et al.*[8] synthesized 2-azacephem derivative 10 and converted it to 11a by treatment with triphenyl phosphine; but desulfurization was accompanied by racemization. The above syntheses failed to obtain the acid (11b) by removing the PNB group of 11a. They also synthesized 13,[9] which lacks the 1-hydroxyethyl group at the 6-position, from 12. Herein we report on the synthesis of 5,[10] an isomer of 4(R'=H).



6 7

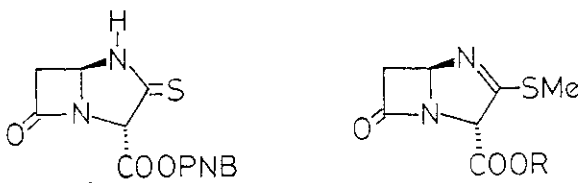


8 9



10

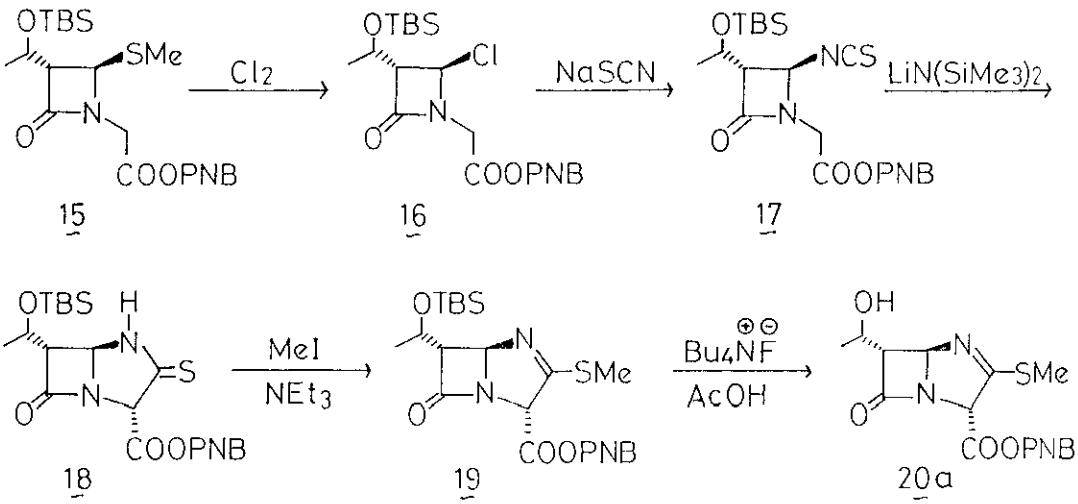
11a R'; PNB
11b R'; H



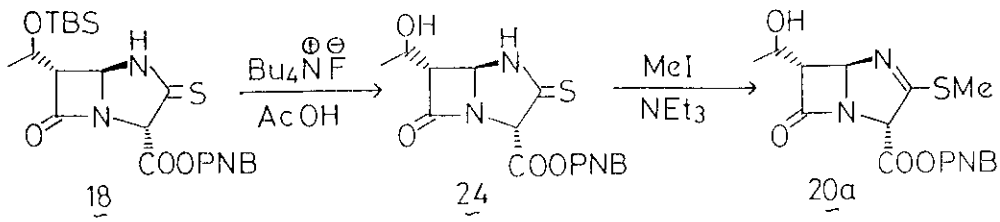
12

13a R; PNB
13b R; H

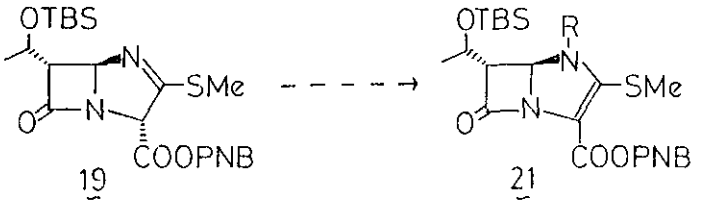
Treatment of 15 with Cl_2 at room temperature gave chloride 16. Compound 16 was refluxed in acetone with sodiun thiocyanate to give isothiocyanate derivative 17 in 69% yield from 15. The absorption at 2020cm^{-1} in the IR spectrum indicated the presence of the isothiocyanate group, not the thiocyanate group. In the proton NMR ($CDCl_3$) of 17, the coupling constant (2Hz) between H-3 and H-4 of azetidinone strongly suggested the trans stereochemistry. Treatment of 17 with lithium hexamethyldisilazide at -78°C and subsequent work up gave 18 in 71% yield. Absorption at 1790cm^{-1} in the IR spectrum strongly suggested the bicyclic thiolactam structure of 17. Treatment of 18 with methyl iodide in the presence of triethylamine at room temperature gave 19 in 94% yield. IR absorption at 1570cm^{-1} indicated S-methylation, and not N-methylation.

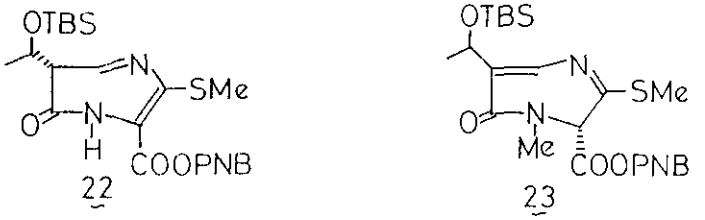


Deprotection of alcohol of 19 by tetrabutylammonium fluoride in acetic acid gave 20a albeit in poor yield, probably due to the instability of 19 to acid. Thus the alcohol was deprotected in advance. Treatment of 18 with tetrabutylammonium fluoride in acetic acid gave 24 in 83% yield. Methylation of 24 (methyl iodide and triethylamine) gave 20a(mp 95-96°C) in 80% yield.

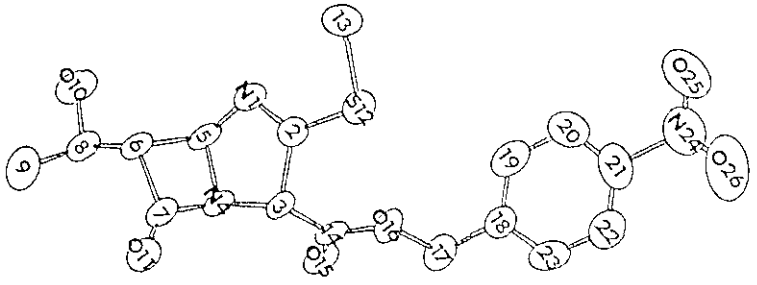


The conversion of 19 to 21 by treatment with base and alkyl or acyl halide were attempted. As the base triethylamine, DBU, sodium hydride, potassium hydride and lithium hexamethyldisilazide, and as the halide methyl iodide and acetyl chloride were examined, but 21 was not obtained in any case. When 19 was treated with potassium hydride and methyl iodide, 22 and 23 were obtained. Under the other conditions, only recovery of 19 was observed.





To determine the absolute stereochemistry at C-3, 20a was analyzed by X-ray diffraction. The space group of 20a is C2, with a=29.606, b=4.567, c=15.165Å, β=103.14° and z=4. The intensity data for 1912 reflections were collected on a RIGAKU automatic four circle diffractometer using Cu-Kα radiation and the 2θ-ω scan technique up to 2θ<128°. The structure was solved by the heavy atom method and refined to an R factor of 9.5%. A view of the molecule is as shown in Fig. 1.



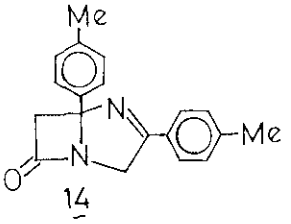
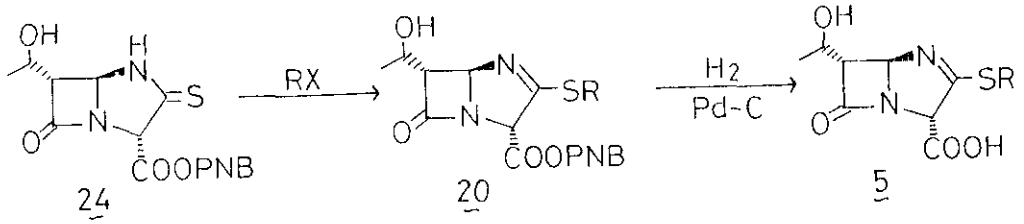


Fig. 1

The absolute stereochemistry at C-3 is S and at C-5 is R. The height of the pyramid formed by C-3, C-5, C-7 and apical N is 0.535Å. The value is larger than that of the penem, and corresponds to that of the carbapenem.[11] Comparison with the azapenem compound 14, which had already been analyzed by X-ray diffraction,[12] showed the conformation of 20a to be similar.

Hydrogenolysis of 20a with 10% Pd-C catalyst gave 5a(R=CH_3) in 51% yield. Other examples are summarized in Table 1.



24 20 5

Table 1

The yield of 20 and 5

entry	RX	20	5
a	MeI	80%	51%
b	EtI	35	51
c	ICH_2CN	97	39
d	$BrCH_2CO_2Et$	84	51

Compound 5a showed a weak antibacterial activity only to *Staphylococcus aureus*.

EXPERIMENTAL

IR spectra were recorded on a Jasco A-102 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian XL-100A or a Varian EM-360L spectrometer. Chemical shifts are reported in parts per million (δ) using, unless otherwise specified, tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a JEOL JMS-01SG spectrometer.

p-Nitrobenzyl (3S,4R)-3-[(R)-1-*tert*-Butyldimethylsilyloxyethyl]-4-isothiocyanato-2-oxoazetidine-1-ylacetate (17)

A solution of 15 (1.01g) in methylene chloride (20ml) was treated with a solution of chlorine in carbon tetrachloride at 0°C for 10 min. The solvent was evaporated

in vacuo. To the residual syrup acetone (20ml) and sodium thiocyanate (0.95g) were added, and the mixture was refluxed for 1 h. The mixture was poured into water and extracted with ethyl acetate. The ethyl acetate extract was dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (3:1) to give 17 (0.71g) as an oil. Yield 69%. NMR($CDCl_3$)δ 0.05(3H, s), 0.08(3H, s), 0.87(9H, s), 1.28(3H, d, J=6Hz), 3.31(1H, dd, J=5, 2Hz), 3.90(1H, d, J=18Hz), 4.15(6H, dq, J=6, 5Hz), 4.26(1H, d, 18Hz), 5.26(2H, s), 5.41(1H, d, J=2Hz), 7.48,8.20(4H, AB-q, J=9Hz). IR($CHCl_3$) 2020, 1780, 1760cm^{-1}.

p-Nitrobenzyl (2S,5R,6S)-6-[(R)-1-*tert*-Butyldimethylsilyloxyethyl]-7-oxo-3-thioxo-1,4-diazabicyclo[3.2.0]heptane-2-carboxylate (18)

To a solution of hexamethyldisilazane (580μl) in tetrahydrofuran (10ml) was added a solution of n-BuLi in hexane (1.7ml, 1.63mmol/ml) at 0°C with stirring. The mixture was stirred for 10 min at the same temperature, and then a solution of 17 (650ml) in tetrahydrofuran (15ml) was added dropwise at -78°C. After being stirred at -78°C for 30 min, acetic acid (1ml) was added. The mixture was poured into water and extracted with methylene chloride. The methylene chloride extract was evaporated *in vacuo* and the residue obtained was chromatographed on silica gel eluting with hexane-ethyl acetate (4:1) to give 18 (459mg) as an oil. Yield 71%. NMR($CDCl_3$)δ 0.08(6H, s), 0.87(9H, s), 1.25(3H, d, J=6Hz), 3.32(1H, dd, J=5, 2Hz), 4.21(1H, dq, J=6, 5Hz), 5.18(1H, d, J=2Hz), 5.28(2H, s), 5.38(1H, t, J=2Hz), 7.50,8.19(4H, AB-q, J=9Hz), 8.86(1H, broad s). IR($CHCl_3$) 3400, 1790, 1750, 1470cm^{-1}.

p-Nitrobenzyl (2S,5R,6S)-6-[(R)-1-*tert*-Butyldimethylsilyloxyethyl]-3-methylthio-7-oxo-1,4-diazabicyclo[3.2.0]hept-3-ene-2-carboxylate (19)

A solution of 18 (729mg) in methylene chloride (20ml) was treated with methyl iodide (118μl) and triethylamine (228μl) at 0°C for 1 h. The mixture was washed with water and sat. brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (4:1) to give 19 (707mg) as colorless crystals, mp 98.5-99.5°C. Yield 94%. NMR($CDCl_3$)δ 0.08(6H, s), 0.89(9H, s), 1.30(3H, d, J=7Hz), 2.53(3H, s), 3.12(1H, dd, J=5, 2Hz), 4.29(1H, dq, J=7, 5Hz), 5.15(1H, d, J=2Hz), 5.24(2H, s), 5.60(1H, t, J=2Hz), 7.51,8.22(4H, AB-q, J=9Hz). IR($CHCl_3$) 1785, 1760, 1570cm^{-1}.

Anal. Calcd for $C_{22}H_{31}N_3O_6SiS$: C, 53.53; H, 6.33; N, 8.51; S, 6.49. Found: C, 53.47; H, 6.36; N, 8.43, S, 6.61.

p-Nitrobenzyl 5S-5-[(R)-1-*tert*-Butyldimethylsilyloxyethyl]-2-methylthio-6-oxo-3,7-diazacyclohept-1,3-diene-1-carboxylate (22) and *p*-Nitrobenzyl 1S-5-[(R)-1-*tert*-Butyldimethylsilyloxyethyl]-7-methyl-2-methylthio-6-oxo-3,7-diazacyclohept-2,4-diene-1-carboxylate (23)

To a suspension of KH (9.6mg) in tetrahydrofuran (1ml) was added a solution of 19 (80.6mg) in tetrahydrofuran (1ml) at room temperature. The mixture was stirred for 5 min, then methyl iodide (20µl) was added. After being stirred at room temperature for 1 h, the mixture was treated with acetic acid and poured into water, and extracted with ethyl acetate. The ethyl acetate extract was dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (4:1-2:1) to give 22 (17mg, yield 21%) as an oil and 23 (15mg, yield 18%) as an oil.

22: NMR($CDCl_3$)δ 0.17(6H, s), 0.90(9H, s), 1.36(3H, d, J=6Hz), 2.30(3H, s), 2.57 (1H, dd, J=8, 6Hz), 4.64(1H, dq, J=8, 6Hz), 5.37(2H, s), 7.41(1H, d, J=6Hz), 7.67, 8.23(4H, AB-q, J=9Hz). IR($CHCl_3$) 1685, 1610, 1525cm^{-1}. MS m/e 493(M).

23: NMR($CDCl_3$)δ 0.05(3H, s), 0.12(3H, s), 0.95(9H, s), 1.06(3H, d, J=6Hz), 2.52 (3H, s), 3.21(3H, s), 4.39(1H, s), 5.03(1H, q, J=6Hz), 5.03(1H, d, J=14Hz), 5.38 (1H, d, J=14Hz), 7.22(1H, s), 7.44,8.22(4H, AB=q, J=9Hz). IR($CHCl_3$) 1750, 1630, 1600, 1515cm^{-1}. MS m/e 507(M).

p-Nitrobenzyl (2S,5R,6S)-6-[(R)-1-Hydroxyethyl]-7-oxo-3-thioxo-1,4-diazabicyclo-[3.2.0]heptane-2-carboxylate (24)

A solution of 18 (1.08g) in tetrahydrofuran (20ml) was treated with tetrabutylammonium fluoride (2.36g) and acetic acid (1.3ml) at 30°C for 20 h. The mixture was diluted with ethyl acetate and washed with water, 5% sodium bicarbonate and sat. brine solutions, and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (1:4) to give 24 (686mg) as an oil. Yield 83%. NMR($CDCl_3$-CD_3OD)δ 1.32(3H, d, J=6Hz), 3.27(1H, dd, J=7, 2Hz), 4.11(1H, dq, J=7, 6Hz), 5.19(1H, d, J=2Hz), 5.30(3H, broad s), 7.56,8.24(4H, AB-q, J=9Hz). IR(neat) 3300, 1790, 1750, 1490cm^{-1}.

p-Nitrobenzyl (2S,5R,6S)-6-[(R)-1-Hydroxyethyl]-3-methylthio-7-oxo-1,4-diazabicyclo[3.2.0]hept-3-ene-2-carboxylate (20a)

A:From 24. A solution of 24 (647mg) in methylene chloride (10ml) was treated with methyl iodide (170µl) and triethylamine (370µl) at 0°C for 1 h. The mixture was washed with water and sat. brine, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue obtained was chromatographed on silica gel eluting with hexane-ethyl acetate (1:4) to give 20a (707mg) as colorless crystals, mp 95-96°C. Yield 94%. NMR($CDCl_3$)δ 1.39(3H, d, J=6Hz), 2.53(3H, s), 3.15(1H, dd, J=6, 2Hz), 4.31(1H, pent, J=6Hz), 5.19(1H, d, J=3Hz), 5.61(1H, t, J=3Hz), 7.50,8.22(4H, AB-q, J=9Hz). IR($CHCl_3$) 1780, 1750, 1565cm^{-1}. Anal. Calcd for $C_{16}H_{17}N_3O_6S$: C, 50.65; H, 4.52; N, 11.08; S, 8.45. Found: C, 50.61, H, 4.53, N, 11.11; S, 8.40.

B:From 19. Compound 19 was treated with tetrabutylammonium fluoride and acetic acid, and worked up as described in the case of 24 to give 20a in a yield of 5%.

Sodium (2S,5R,6S)-6-[(R)-1-Hydroxyethyl]-3-methylthio-7-oxo-1,4-diazabicyclo-[3.2.0]hept-3-ene-2-carboxylate (5a)

A mixture of 20a (100mg) in a solution of tetrahydrofuran (10ml) and 0.1M phosphate buffer (pH 7, 10ml) was shaken with 10% Pd-C for 20 h under a hydrogen atmosphere. After removal of the catalyst by filtration through celite, the filtrate was washed with ethyl acetate, and concentrated *in vacuo* to a half volume, and chromatographed on a column of Diaion CHP-20P (Mitsubishi Chemical Industries, Ltd.) eluting with water to give 5a (36mg) as a powder. Yield 51%. NMR(100MHz, D_2O/TSP)δ 1.37(3H, d, J=6Hz), 2.52(3H, s), 3.33(1H, dd, J=6, 2Hz), 4.32(1H, pent, J=6Hz), 5.17(1H, d, J=3Hz), 5.60(1H, t, J=3Hz). IR(KBr) 3400, 1775, 1620, 1560cm^{-1}.

p-Nitrobenzyl (2S,5R,6S)-3-Ethylthio-6-[(R)-1-hydroxyethyl]-7-oxo-1,4-diazabicyclo[3.2.0]hept-3-ene-2-carboxylate (20b)

Compound 24 was treated with ethyl iodide and triethylamine, and worked up as described in the case of 20a to give 20b in a yield of 35%. NMR($CDCl_3$)δ 1.35(3H, t, J=7Hz), 1.40(3H, d, J=6Hz), 3.13(2H, q, J=7Hz), 3.18(1H, dd, J=6, 3Hz), 3.9-4.6(1H, m), 5.17(1H, d, J=3Hz), 5.27(2H, s), 5.61(1H, t, J=3Hz), 7.51,8.23(4H, AB-q, J=9Hz). IR($CHCl_3$) 1780, 1750, 1565cm^{-1}.

Sodium (2S,5R,6S)-3-Ethylthio-6-[(R)-1-hydroxyethyl]-7-oxo-1,4-diazabicyclo-[3.2.0]hept-3-ene-2-carboxylate (5b)

Compound 20b was treated with H_2/10%Pd-C, and worked up as described in the case of 5a to give 5b in a yield of 51%. NMR(100MHz, D_2O/TSP)δ 1.35(3H, t, J=7Hz), 1.39(3H, d, J=6Hz), 3.12(2H, q, J=7Hz), 3.36(1H, dd, J=6, 2Hz), 4.34(1H, pent, J=6Hz), 5.15(1H, d, J=3Hz), 5.62(1H, t, J=3Hz). IR(KBr) 3400, 1775, 1620, 1560cm^{-1}.

p-Nitrobenzyl (2S,5R,6S)-3-Cyanomethylthio-6-[(R)-1-hydroxyethyl]-7-oxo-1,4-diaza-bicyclo[3.2.0]hept-3-ene-2-carboxylate (20c)

Compound 24 was treated with iodoacetonitrile and triethylamine, and worked up as described in the case of 20a to give 20c in a yield of 97%. NMR($CDCl_3$)δ 1.40(3H, d, J=6Hz), 3.25(1H, dd, J=6, 2Hz), 3.92(2H, s), 4.33(1H, pent, J=6Hz), 5.28(1H, d, J=2Hz), 5.30(2H, s), 5.69(1H, t, J=2Hz), 7.52,8.23(4H, AB-q, J=9Hz). IR($CHCl_3$) 2250, 1780, 1760, 1580cm^{-1}.

Sodium (2S,5R,6S)-3-Cyanomethylthio-6-[(R)-1-hydroxyethyl]-7-oxo-1,4-diazabicyclo-[3.2.0]hept-3-ene-2-carboxylate (5c)

Compound 20c was treated with H_2/10%Pd-C, and worked up as described in the case of 5a to give 5c in a yield of 39%. NMR(100MHz, D_2O/TSP)δ 1.37(3H, d, J=6Hz), 3.42(1H, dd, J=6, 2Hz), 4.08(2H, s), 4.36(1H, pent, J=6Hz), 5.27(1H, d, J=2Hz), 5.66(1H, t, J=2Hz). IR(KBr) 3400, 2250, 1770, 1625, 1570cm^{-1}.

p-Nitrobenzyl (2S,5R,6S)-3-Ethoxycarbonylmethyl-6-[(R)-1-hydroxyethyl]-7-oxo-1,4-diazabicyclo[3.2.0]hept-3-ene-2-carboxylate (20d)

Compound 24 was treated with ethyl bromoacetate and triethylamine, and worked up as described in the case of 20a to give 20d in a yield of 84%. NMR($CDCl_3$)δ 1.29(3H, t, J=7Hz), 1.39(3H, d, J=6Hz), 3.17(1H, dd, J=6, 2Hz), 3.92(2H, s), 3.9-4.6(3H, m), 5.23(1H, d, J=3Hz), 5.28(2H, s), 5.60(1H, t, J=3Hz), 7.54,8.24(4H, AB-q, J=9Hz). IR($CHCl_3$) 1780, 1750, 1740, 1570cm^{-1}.

Sodium (2S,5R,6S)-3-Ethoxycarbonylmethyl-6-[(R)-1-hydroxyethyl]-7-oxo-1,4-diaza-bicyclo[3.2.0]hept-3-ene-2-carboxylate. (5d)

Compound 20d was treated with H_2/10%Pd-C, and worked up as described in the case of 5a to give 5d in a yield of 51%. NMR(100MHz, D_2O/TSP)δ 1.27(3H, t, J=7Hz),

1.35(3H, d, J=6Hz), 3.27(1H, dd, J=6, 2Hz), 4.00(2H, s), 4.25(2H, q, J=7Hz), 4.32(1H, pent, J=6Hz), 5.22(1H, d, J=3Hz), 5.57(1H, t, J=3Hz). IR(KBr) 3400, 1775, 1740, 1620, 1565cm^{-1}.

REFERENCES

1. R.B.Woodward, 'Recent Advances in the Chemistry of β-lactam Antibiotics', eds.by J.Elks, London 1977, the Chemical Society, Special publication 28, chapter 18.
2. H.Kropp, J.S.Kahan, F.M.Kahan, J. Sandelof, G.Darland and J.Birnbaum, Abstract of 16th Intersci.Conf.Antimicrob.Agent and Chemother., P. 228, Chicago, 1976.
3. Recent reports in this field are summarized in 'Topics in Antibiotic Chemistry', Vol 3 and 4, eds.by P.G.Sammes, Ellis Horwood, Chichester, 1980.
4. (a)T.Tanaka, T.Hashimoto, K.Iino, Y.Sugimura and T.Miyadera Tetrahedron Lett., 23, 1075(1982). (b)*idem*, J.Chem.Soc.,Chem.Commun., 1982, 713.
5. T.Miyadera, Y.Sugimura, T.Hashimoto, T.Tanaka, K.Iino, T.Shibata and S.Sugawara, J.Antibiotics, 36, 1034(1983).
6. I.Nagakura, Heterocycles, 16, 1495(1981).
7. H.Alper, C.P.Perera and F.R.Ahmed, J.Am.Chem.Soc., 103, 1289(1981).
8. G.Johnson and B.C.Ross, J.Chem.Soc.,Chem.Commun., 1981, 1269.
9. *Idem*, *ibid.*, 1984, 970.
10. These results were briefly communicated at the 104th Annual Meeting of the Pharmaceutical Society of Japan (1984). T.Shibata, Y.Sugimura, S.Sato and K.Kawazoe, Abstract of 104th Annual Meeting of Pharmaceutical Society of Japan, 28A3-3, Sendai, March 1984.
11. M.Lang, K.Prasad, W.Holick, J.Gosteli, I.Ernest and R.B.Woodward, J.Am.Chem. Soc., 101, 6296(1979).
12. F.R.Ahmed, Acta Cryst., C39, 735(1983).

Received, 30th July, 1985