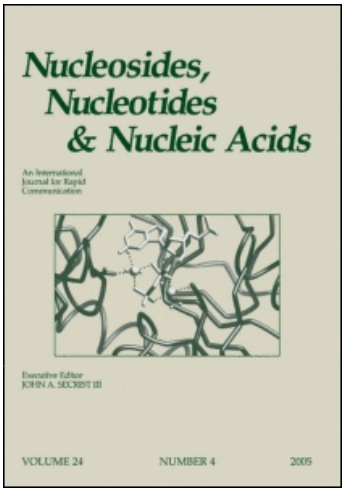


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Nucleosides VI: A Novel and Convenient Synthesis of Purine *S*-Cyclonucleosides Via Mitsunobu Reaction

Ji-Wang Chern[a]; Chia-Chi Kuo[a]; Ming-Jyh Chang[a]; Lee-Tai Liu[a]
[a] Medical Laboratories, Institute of Pharmacy, National Defense Medical Center, Taipei, Taiwan Republic of China

To cite this Article Chern, Ji-Wang , Kuo, Chia-Chi , Chang, Ming-Jyh and Liu, Lee-Tai(1993) 'Nucleosides VI: A Novel and Convenient Synthesis of Purine *S*-Cyclonucleosides Via Mitsunobu Reaction', Nucleosides, Nucleotides and Nucleic Acids, 12: 9, 941 — 949
To link to this Article: DOI: 10.1080/07328319308018564
URL: http://dx.doi.org/10.1080/07328319308018564

NUCLEOSIDES & NUCLEOTIDES, 12(9), 941-949 (1993)

NUCLEOSIDES VI: A NOVEL AND CONVENIENT SYNTHESIS OF PURINE *S*-CYCLONUCLEOSIDES VIA MITSUNOBU REACTION

Ji-Wang Chern*, Chia-Chi Kuo, Ming-Jyh Chang and Lee-Tai Liu
Medical Laboratories and Institute of Pharmacy, National Defense Medical Center, P. O. Box 90048-512, Taipei, Taiwan, Republic of China (100)

ABSTRACT: Two representative *S*-cyclonucleosides, 8,5'-anhydro-2',3'-*O*-isopropylidene-8-mercaptoadenosine (**3**) and 8,2'-anhydro-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine (**8**), were prepared in good yields by dropwise addition of one equivalent each of triphenylphosphine and DEAD in DMF into a mixture of 2',3'-*O*-isopropylidene-8-mercaptoadenosine (**2**) or 3',5'-*O*-(tetra-isopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine (**7**), respectively, in DMF. Treatment of compound **2** with two equivalents each of triphenylphosphine and DEAD in DMF afforded *N*-[8,5'-anhydro-2',3'-*O*-isopropylidene-8-mercaptopurin-6-yl]triphenylphospha-λ^5-azene (**4**) in 87% yield.

INTRODUCTION

Purine *S*-cyclonucleosides are important precursors for the synthesis of nucleoside analogues[2] or other deoxynucleosides[3] *via* desulfurization with Raney nickel. There are several approaches available for the preparation of purine *S*-cyclonucleosides involving treatment of 2'-, 3'-, or 5'-*O*-*p*-toluenesulfonyl-8-bromo-[4] or 2',3'-*O*-sulfonyl-8-bromo-[5] derivatives with thiourea or H_2S in pyridine to give the corresponding 8,2'-, 8,3'-, or 8,5'-thiocyclonucleosides

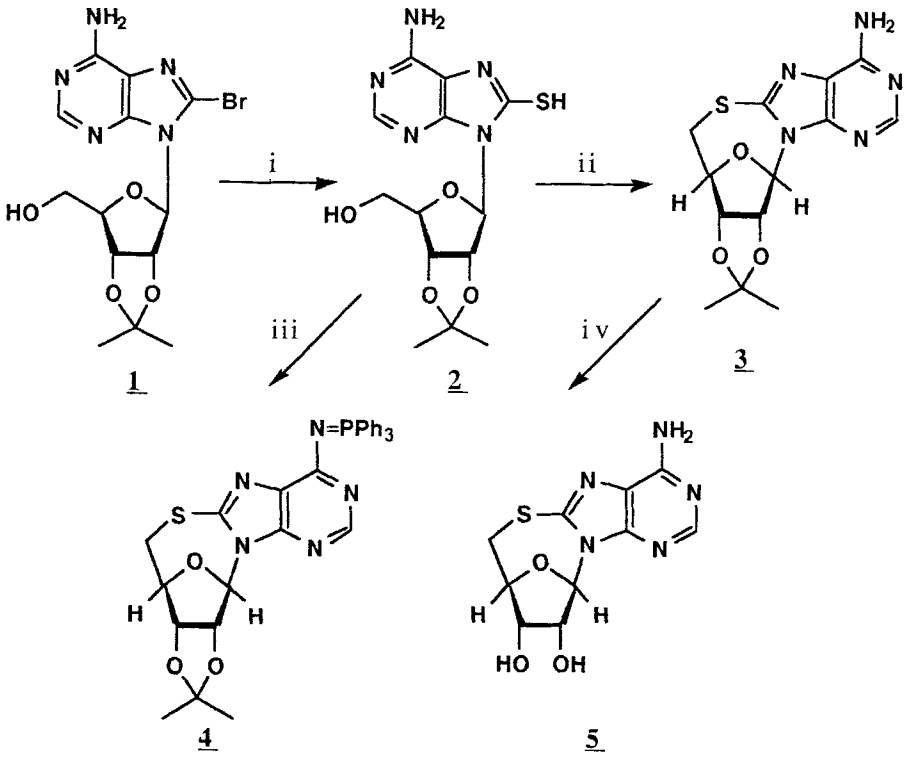
---

This manuscript is dedicated to Professor Leroy B. Townsend on the occasion of his 60th birthday.

respectively. During the course of our ongoing synthetic studies on nucleoside analogues, 8,5'-anhydro-2',3'-*O*-isopropylidene-8-mercaptoadenosine (**3**) is an essential intermediate in the program. A perusal of literature indicated that a direct treatment of 5'-tosylated 8-bromoadenosine with thiourea did not lead to the synthesis of compound **3** because of rapid cyclization to the N^3 position of purine.[6] However, compound **3** could only be prepared at low temperature to avoid formation of a N^3-5'-cyclized product by careful treatment of **2** with hydrogen sulfide or aqueous sodium hydrogen sulfide in pyridine.[7] Since a hydroxyl group can be replaced by a wide range of nucleophiles using the Mitsunobu reaction[8], we reasoned that 2',3'-*O*-isopropylidene-8-mercaptoadenosine (**2**) under Mitsunobu conditions would lead to the formation of **3**. We now report herein rapid cyclization of 8-mercaptopurine nucleosides containing one hydroxyl group available on the suitably protected ribose moiety by the Mitsunobu reaction.

RESULTS AND DISCUSSION

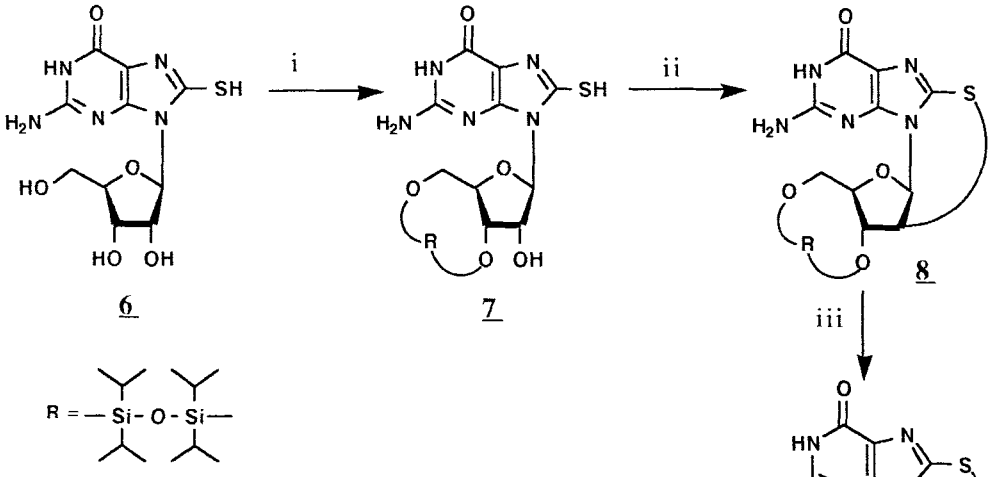
Compound **2**, which was prepared in 51% yield by reaction of 2',3'-*O*-isopropylidene-8-bromoadenosine (**1**)[9] with thiourea in ethanol at reflux, was treated with two equivalents each of triphenylphosphine and diethyl azodicarboxylate (DEAD) in dry DMF at room temperature. The starting material was completely converted to only one product in 5 minutes. This product was isolated by column chromatography and the structure of this product was determined to be *N*-[8,5'-anhydro-2',3'-*O*-isopropylidene-8-mercaptopurin-6-yl]triphenylphospha-λ^5-azene (**4**) in 87% yield instead of 8,5'-anhydro-2',3'-*O*-isopropylidene-8-mercaptoadenosine (**3**) on the basis of ^{1}H NMR, mass spectral data and elemental analysis. By a careful examination of the reaction process, we observed that two products (with R_f = 0.44 and 0.94, solvent system: $CHCl_3$/MeOH = 95/5) were formed at the very beginning and the more polar product (R_f = 0.44) was then rapidly converted to the less polar product (R_f = 0.94). When the same reaction was carried out by the use of one equivalent each of DEAD and triphenylphosphine, the reaction did not go to completion and afforded a mixture of compounds **3** and **4**.



i, thiourea/EtOH, reflux, 2 h, 51%; ii, one equivalent of each DEAD and PPh_3 in DMF, r.t, 5 min., 68%; iii, two equivalents of each DEAD and PPh_3 in DMF, r.t, 5 min, 87%; iv, Dowex-50W, MeOH, 50° C, 3 h, 30%.

It has been reported that amines under Mitsunobu conditions would lead to the formation of *N*-phosphinephospha-λ^5-azenes.[10] Thus, we assumed that this reaction might proceed through an initial formation of compound **3** which subsequently reacted with an excess amount of triphenylphosphine to furnish compound **4**. In a view of the quick ring closure of compound **2** under Mitsunobu conditions and in order to obtain compound **3**, one equivalent each of triphenylphosphine and DEAD in DMF was dropwise added to a solution of compound **2** in DMF. As a result, compound **3** was obtained in 70% yield. Treatment of compound **3** with Dowex-50W (H^+) in methanol afforded 8,2'-anhydro-8-mercaptoadenosine (**5**) in 30% yield. To our

best knowledge, the preparation of purine *S*-cyclonucleosides *via* the Mitsunobu reaction has not been reported.



6 7 8 9

i, 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, DMF/pyridine, r.t., 24 h, 92%; ii, one equivalent of DEAD and PPh_3/toluene, 10 min., 71%; iii Bu_4NF/toluene, r.t., 7 h, 61%.

To further explore the application of this methodology, 3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine (**7**), which was prepared in 92% yield from a reaction of 8-mercaptoguanosine (**6**)[11] with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, was analogously treated with DEAD and triphenylphosphine in toluene leading to the formation of 8,2'-anhydro-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine (**8**) in 71% yield. The structure of compound **8** was assigned on the basis of ^1H- and ^{13}C-NMR spectral data and elemental analysis. Subsequent treatment of compound **8** with tetrabutylammonium fluoride afforded 8,2'-anhydro-8-mercaptoguanosine (**9**) in 61% yield.

In summary, we have shown that the rapid cyclization of 8-mercaptopurine nucleosides under Mitsunobu conditions (*vide supra*) is a valuable synthetic route to the preparation of purine *S*-cyclonucleosides.

EXPERIMENTAL SECTION

Melting points were obtained on an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on an either Jeol FX-100 or Jeol JNM-EX400 spectrometer from National Taiwan Normal University or on a Bruker Model AM 300 spectrometer from National Taiwan University, Taipei, and are reported in parts per million with DMSO-d_6 as internal standard on a δ scale. EI mass spectra was recorded on Jeol JMS-D100 mass spectrometer from National Taiwan University. Elemental analyses for C, H, and N were carried out either on a Heraeus Elemental Analyzer in Cheng-Kong University, Tainan, or on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University, Taipei and were within ± 0.4 % of the theoretical values.

2',3'-*O*-Isopropylidene-8-bromoadenosine (1). A mixture of 8-bromoadenosine[3] (1.73 g, 5.0 mmol) and p-toluenesulfonic acid monohydrate (1.05 g, 6.1 mmol) in acetone (20 mL) was added to triethyl orthoformate (3.2 mL). The solution was stirred at room temperature for 1 h. The pH value of the mixture was then adjusted to 8 by 28% ammonia water to get white precipitate. The white solid was collected by filtration and recrystallized from H_2O to furnish compound **1** (1.2 g, 62%). mp 220 °C [lit.[9] 221-222 °C]. ^1H NMR (300 MHz, DMSO-d_6): δ 1.32 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 3.50 (m, 2 H, 5'-CH_2), 4.16 (m, 1 H, 4'-H), 5.02 (m, 1 H, 3'-H), 5.10 (t, J = 5.8 Hz, 1H, 5'-OH), 5.65 (m, 1 H, 2'-H), 6.01 (d, J = 2.5 Hz, 1'-H), 7.52 (s, 2 H, NH_2), 8.14 (s, 1H, 2'-H); ms: m/z 368 (M^+).

2',3'-*O*-Isopropylidene-8-mercaptoadenosine (2). A mixture of compound **1** (2.9 g, 7.7 mmol) and thiourea (0.7 g, 9.3 mmol) in anhydrous EtOH (50 mL) was refluxed in an oil bath for 3 h. The solvent was then evaporated *in vacuo* (50 °C) to oily residue. The residue was then applied to column chromatography (silica gel: 2 x 20 cm; solvent system: $CHCl_3$/MeOH = 95/5). The desired fraction (R_f=0.2, $CHCl_3$) was collected to furnish compound **2** (1.33 g, 51%). An analytical sample was recrystallized from ethanol. mp 166 °C (dec.). ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 3.48 (m, 2 H, 5'-CH_2), 4.09 (d, J=3 .48 Hz, 1 H, 4'-CH), 4.97 (m, 1 H, 3'-

H), 5.45 (m, 1 H, 2'-H), 6.52 (d, J = 2.3 Hz, 1 H, 1'-H), 7.00 (s, 2 H, NH_2), 8.13 (s, 1 H, 2-CH), 12.61 (s, 1 H, SH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 25.69, 27.59, 62.13, 79.53, 82.02, 82.41, 87.11, 89.22, 107.38, 113.50, 148.27, 152.67, 167.51. ms: m/z 339 (M^+). Anal. Calcd for $C_{13}H_{17}N_5SO_4$: C, 46.01; H, 5.05; N, 20.63. Found: C, 45.98; H, 4.95; N, 20.59.

8,5'-Anhydro-2',3'-*O*-isopropylidene-8-mercaptoadenosine (3). To a solution of compound **2** (0.5 g, 1.47 mmol) in DMF (15 mL) was gradually added a mixture of diethyl azodicarboxylate (0.26 g, 1.50 mmol) and triphenylphosphine (0.39 g, 1.50 mmol) within 5 min. The mixture was then evaporated *in vacuo* (50 °C) and the residue was applied to column chromatography (silica gel: 2.5 x 20 cm; solvent system: chloroform/methanol: 95/5). The desired fraction (R_f = 0.44, $CHCl_3$/MeOH = 95/5) was collected and evaporated *in vacuo* to furnish compound **3** (0.33 g, 68%). An analytical sample was recrystallized from $CHCl_3$, mp 269 °C (dec.) [lit.[7], 269 °C]. ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 3.22 (s, 2 H, 5'-CH_2), 4.97 (d, J = 2.2 Hz, 1 H, 4'-CH), 5.07 (d, J = 5.8 Hz, 1 H, 3'-CH), 5.12 (d, J = 5.6 Hz, 1 H, 2'-CH), 6.26 (s, 1 H, 1'-H), 7.38 (s, 2 H, NH_2), 8.14 (s, 1 H, 2-CH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 24.71, 26.44, 34.60, 83.91, 85.61, 86.11, 88.22, 112.15, 118.50, 144.70, 150.96, 153.22, 155.42; ms: m/z 321 (M^+).

***N*-[8,5'-Anhydro-2',3'-O-isopropylidene-8-mercaptopurin-6-yl]-triphenylphospha-λ^5-azene (4).** To a mixture of compound **2** (1.3 g, 3.83 mmol) in DMF (10 mL) were added DEAD (1.34 g, 7.7 mmol) and triphenylphosphine (2.0 g, 7.63 mmol). The mixture was stirred at room temperature for 5 min and the solvent was then evaporated *in vacuo* (50 °C) to dryness. To the residue was added ether (10 mL) to give white solid which was collected by filtration. The crude product was recrystallized from EtOH to give compound **4** (2.28 g, 87%). mp 345 °C (dec.), ^1H NMR (300 MHz, DMSO-d_6): δ 1.31 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 3.19 (m, 2 H, 5'-CH_2), 4.96 (s, 1 H, 4'-H), 5.10 (br s, 2 H, 3'-H & 2'-H), 6.21 (s, 1 H, 1'-H), 7.63 (m, 15 H, 3 C_6H_5), 7.93 (s, 1 H, 2-CH); ^{13}C NMR (50 MHz, DMSO-d_6): δ 24.72, 26.47, 34.63, 83.96, 85.69, 86.06, 88.21, 112.12, 128.05, 129.09, 129.25,

129.38, 131.79, 131.92, 132.39, 132.70, 133.03, 133.17, 144.30, 151.41, 151.49, 151.89; ms: *m/z* 582 (M^+). Anal. Calcd for $C_{31}H_{28}N_5O_3PS$: C, 64.02; H, 4.85; N, 12.04. Found: C, 64.03; H, 4.95; N, 12.14.

8,2'-Anhydro-8-mercaptoadenosine (5). To a mixture of compound **3** (0.1 g, 0.3 mmol) in methanol (5 mL) was added Dowex-50W (H^+) (1.0 g). The mixture was heated at 50 °C for 3 h and the solvent was then neutralized with 28% ammonia water to arrang the mixture to pH 8.0. The resin was filtered off and the filtrate was concentrated *in vacuo* (50 °C) to dryness. To the residue was added ethyl acetate (10 mL) to get solid which was collected by filtration and was recrystallized from methanol to give compound **5** (26 mg, 30%). mp 214 °C [lit.[7] 213-215 °C]. ^1H NMR (300 MHz, DMSO-d_6): δ 3.16 (m, 2 H, 5'-CH_2), 4.36 (t, J = 5.23 Hz, 1 H, 4'-CH), 4.66 (t, J = 7.43 Hz, 3'-CH), 4.79 (s, 1 H, 2'-CH), 5.30 (d, J = 4.5 Hz, 1 H, 3'-OH), 5.63 (d, J =7.1 Hz, 1 H, 2'-OH), 6.17 (s, 1 H, 1'-CH), 7.33 (s, 2 H, NH_2), 8.13 (s, 1 H, 2-CH).

8-Mercaptoguanosine (6). A mixture of 8-bromoguanosine[11] (10.3 g, 32.2 mol) and thiourea (4.9 g, 64.37 mol) in anhydrous ethanol (100 mL) was refluxed in an oil bath for 24 h. After the mixture was cooled to room temperature, the solid was filtered b y filtration and the crude product was recrystallized from ethanol to give compound **6** (7.43 g, 82%). mp 218 °C (dec.) [lit.[11] mp 220 °C (dec.)]; ^{13}C NMR (75 MHz, DMSO-d_6): δ 62.43, 70.45, 70.65, 85.21, 88.84, 104.21, 149.62, 151.03, 153.59, 165.85.

3',5'-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine (7). To a mixture of compound **6** (1.24 g, 3.93 mmol) in dried pyridine (12 mL) and DMF (4 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (1.36 mL, 4.32 mmol). The mixture was allowed to stir at room temperature for 16 h and the solution was then pourred into an ice water (250 mL). The white solid was collected by filtration and recrystallized from a mixture of ethanol and water to give compound 7 (2.01 g, 92%). mp 225 °C (dec.); ^1H NMR (300 MHz, DMSO-d_6): δ 3.51 (m, 2 H, 5'-H), 3.64 (d, 1 H, 4'-H),

3.80-4.94 (m, 3 H, 2'-H, 3'-H, 2'-OH), 6.25 (d, 1 H, 1'-H), 6.58 (br s, 2 H, NH_2), 11.08 (s, 1 H, NH), 12.89 (s, 1 H, SH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.00, 12.17, 12.37, 12.60, 12.79, 13.01, 16.78, 16.91, 17.03, 17.17, 17.25, 17.35, 62.33, 70.40, 71.21, 81.08, 89.08, 103.97, 149.68, 150.88, 153.67, 164.91. Anal. Calcd for $C_{22}H_{39}N_5O_6SSi_2 \cdot H_2O$: C, 45.89; H, 7.18; N, 12.16. Found: C, 46.16; H, 7.22; N, 11.92.

8,2'-Anhydro-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-8-mercaptoguanosine (8) was prepared in 71% yield by a similar approach which afforded compound **3**. An analytical sample was recrystallized from a mixture of EtOH and H_2O. mp 202-204 °C ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (m, 2 H, 5'-H), 3.92 (m, 1 H, 4'-H), 4.48 (t, J = 7.3 Hz, 1 H, 3'-H), 4.85 (t, J = 6.8 Hz, 1 H, 2'-H), 6.25 (d, J = 7.1 Hz, 1 H, 1'-H), 6.54 (s, 2 H, NH_2, D_2O exchangeable), 10.64 (br s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.83, 11.89, 12.43, 12.91, 16.77, 16.91, 16.99, 17.12, 60.15, 60.68, 79.53, 81.90, 84.34, 121.59, 146.60, 150.88, 153.45, 155.28.; ms: m/z 539 (M^+). Anal. Calcd for $C_{22}H_{37}N_5O_5SSi_2 \cdot 1/2\,H_2O$: C, 48.15; H, 6.98; N, 12.76. Found: C, 48.34; H, 6.86; N, 12.75.

8,2'-Anhydro-8-mercaptoguanosine (9). To a mixture of compound **8** (1.08 g, 2.0 mmol) in dried toluene (15 mL) was added tetrabutylammonium fluoride (1.05 g, 4.00 mmol). The solution was stirred at room temperature for 7 h and the solvent was then evaportaed *in vacuo* (60 °C) to oily residue. To the residue was added methanol (15 mL) and the white solid was collected by filtration. The crude solid was recrystallized from ethanol to furnish compound **9** (0.42 g, 71%). mp >320 °C, ^1H NMR (300 MHz, DMSO-d_6): δ 3.37-3.50 (m, 2 H, 5'-H), 3.89 (q, J = 5.6 Hz, J =9.8 Hz, 1 H, 4'-H), 4.32 (s, 1 H, 3'-H), 4.75 (q, J = 2.4 Hz, J = 6.6 Hz, 1 H, 2'-H), 4.86 (br s, 1 H, 5'-OH, D_2O exchangeable), 5.82 (br s, 1 H, 3'-OH, D_2O exchangeable), 6.26 (d, 1 H, J = 6.5 Hz, 1'-H), 6.52 (s, 2 H, NH_2, D_2O exchangeable), 10.66 (br s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (50 MHz, DMSO-d_6): δ 61.46, 62.40, 77.79, 86.20, 88.15, 121.91, 147.81, 151.17, 153.81, 155.72. Anal. Calcd for $C_{10}H_{11}N_5O_4S \cdot 1/4\,H_2O$: C, 40.05; H, 3.89; N, 23.15. Found: C, 39.80; H, 3.76; N, 23.30.

Acknowledgement

This investigation was supported by a research grant (No. NSC-80-0412-B016-132) from National Science Council of the Republic of China.

REFERENCES

1. Previous paper in this series: Chern, J.-W.; Lee, H.-Y.; Chen, C.-S.; Shewach, D. S.; Daddona, P. E.; Towsend, L. B. *J. Med. Chem.*, **1993**, *36*, 1024.
2. a) Ikehara, M.; Ogiso, Y.; Morri, T. *Tetrahedron*, **1976**, *32*, 43. b) Mizuno, Y.; Kaneko, C.; Oikawa, Y. *J. Org. Chem.*, **1974**, *39*, 1440.
3. Ikehara, M.; Kaneko, M. *Tetrahedron*, **1970**, *26*, 4251.
4. Ikehara, M. *Accounts of Chem. Res.*, **1969**, *2*, 47.
5. a) Blandin, M.; Catlin, J. C. *C. R. Acad. Sci. Ser. D* **1972**, *275*, 1703. b) Ikehara, M.; Kanebo, M.; Sagai, M. *Chem. Pharm. Bull.*, **1968**, *16*, 1151.
6. Ikehara, M.; Tada, H.; Muneyama, K. *Chem. Pharm. Bull.*, **1965**, *13*, 639.
7. Ikehara, M.; Kaneko, M.; Sagai, M. *Tetrahedron*, **1970**, *26*, 5757.
8. Mitsunobu, O. *Synthesis*, **1981**, 1.
9. Ikehara, M.; Tada, H.; Kaneko, M. *Tetrahedron*, **1968**, *24*, 3489.
10. Bittner, S.; Assaf, Y.; Krief, P.; Pomerantz, M.; Ziemnicka, B. T.; Smith, C. G. *J. Org. Chem.*, **1985**, *50*, 1712.
11. Holmes, R. E.; Robins, R. K. *J. Am. Chem. Soc.*, **1965**, *87*, 1772.

Received 4/20/93
Accepted 7/21/93