Studies of Nucleosides and Nucleotides. XXXIV.[1] Purine Cyclonucleosides. 4.[2] Synthesis of a Cyclonucleoside Having an *O* Cyclo Linkage Derived from Guanosine[3]

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Stating from guanosine, the cyclonucleoside, 8,2′-*O*-anhydro-3′-O-methylsulfonyl-5′-*O*-acetyl-8-oxyguanosine, was synthesized. The structure was confirmed by ultraviolet, infrared, and nuclear magnetic resonance absorption spectra in addition to the elemental analyses. In an attempt to obtain 8,5′-*O*-cyclonucleoside, a cyclonucleoside having N^3,5′ linkage was obtained. A convenient method for the synthesis of 2′,3′-*O*-isopropylidene-8-bromoguanosine was described.

Syntheses of purine cyclonucleosides having 8,2′[4-6] and 8,3′[5] cyclo linkages have been reported from our laboratory. In these studies we have chosen adenosine as a starting material, because of its greater solubility in an organic solvent and easier handlings than is the case for guanosine derivatives. Meanwhile a convenient method for the bromination of 2′,3′-*O*-isopropylideneguanosine was developed and it was found that the introduction of a bromine atom in the guanine nucleus increased the solubility in organic solvents of its ribonucleoside. We therefore investigated the cyclization of 8-oxy-2′,3′-di-*O*-mesylguanosine to form the 8,2′-*O*-cyclo linkage. Although the cyclization to form an 8,5′-*S*-cyclonucleoside has been reported[7] previously from the 2′,5′-di-*O*-mesyl-8-mercaptoguanosine, the first synthesis of guanosine *O*-cyclonucleoside is reported in this paper.

In the bromination of guanosine by means of dioxane–bromine,[7] an equivalent amount of hydrobromic acid should be formed in the reaction mixture. We have attempted to use this acid as the catalyst for the acetonation and a direct procedure for the synthesis of 2′,3′-*O*-isopropylidene-8-bromoguanosine (I) has been developed with a satisfactory yield (over-all from guanosine was around 60%). Compound I was then acetylated with acetic anhydride to afford 2′,3′-*O*-isopropylidene-5′-*O*-acetyl-8-bromoguanosine (II) (Scheme I).

Introduction of an 8-hydroxyl group in order to obtain a suitable intermediate for cyclization was achieved by the refluxing II in glacial acetic acid in the presence of sodium acetate.[8] The reaction proceeded with a shift of ultraviolet absorption maxima from 263 mμ to 247 and 294 mμ. Although the product start 2′,3′-*O*-isopropylidene-5′-*O*-acetyl-8-oxyguanosine (III) was a hard syrup, the structure was confirmed by elemental analyses, ultraviolet absorption properties, and the behavior on paper chromatography. Acid-catalyzed removal of the isopropylidene group in III gave 5′-*O*-acetyl-8-oxyguanosine (IV), in which the presence of the 8-keto group was confirmed by an infrared absorption band at 1720 cm^{-1}.[9] The elemental analyses also was consistent with this structure.

Compound IV was then mesylated with 2.2 equiv of methylsulfonylchloride.[11]

As observed in the case of the mesylation of guanosine,[7] the ultraviolet absorption maxima of the dimesyl derivative (V) shifted slightly from 248 and 294 mμ to 254 and 295 mμ. This shift may be attributed to the interaction of methyl sulfonyl residues with the guanine ring as reported for the mesylated uridine.[12] Infrared absorption and elemental analytical data suggested the absence of the mesyl group on the 8-oxy (or 7-NH) group.

The cyclization of 2′,3′-di-*O*-mesyl-5′-*O*-acetyl-8-oxyguanosine (V) was then investigated. Since it was observed previously[6] that the *O* cyclization could be achieved with the attack of a relatively strong nucleophile, sodium acetate in hot dimethylformamide[12] was employed in this case. When compound V was heated at 90–100° (bath temperature) with sodium acetate in dimethylformamide for 4 hr, a compound (VI), which showed ultraviolet absorption maxima at 249 and 286 mμ, was obtained. Although a slight difference in the absorption maxima was recognized between compound VI and 8-methoxyguanosine,[13] the cyclization of the 8-oxy to the 2′ position could be deduced by the analogy with adenine cyclonucleoside.[5,6] The absence of an infrared absorption band at 1720 cm^{-1} and elemental analytical data also supported the occurrence of the cyclization. Nuclear magnetic resonance (nmr) spectra taken in the dimethyl sulfoxide solution showed the absorption peak of $H_{1'}$ proton at τ 6.53 and its coupling constant $J_{H_{1'}-H_{2'}}$ was 5.16 cps. As it was found that in the adenosine series[5,14] the coupling constant $J_{H_{1'}-H_{2'}}$ of 8,2′-(*S* or *O*)-cycloadenosine fell into the range of 5.48–7.0 cps, whereas that of the 8,3′-cyclonucleoside was 2.5 cps. Therefore, the relatively large *J* value found for compound VI might be attributed to the *cis* coupling of the $H_{1'}$ and $H_{2'}$ protons due to the 8,2′ cyclo bond formation. This assumption was further supported by the fact that the 2′-*O*-mesyl group cyclized more easily than the 3′-*O*-mesyl group to form a 2,2′- rather than 2,3′-cyclonucleoside in the pyrimidine nucleoside series.[15,16] It was thus concluded that

(1) Part XXXIII: M. Ikehara, S. Uesugi, and T. Fukui, *Chem. Pharm. Bull.*, **15**, 442 (1967).

(2) Part 3 of this series, M. Ikehara and H. Tada, *ibid.*, **15**, 94 (1967).

(3) A part of this study was presented at the Hokkaido Regional Meeting of Pharmaceutical Society of Japan, 1966.

(4) M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963); **87**, 606 (1965).

(5) M. Ikehara and H. Tada, *Chem. Pharm. Bull.*, **15**, 94 (1967).

(6) M. Ikehara, H. Tada, K. Muneyama, and M. Kaneko, *J. Am. Chem. Soc.*, **88**, 3165 (1966).

(7) M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.*, **13**, 639 (1965).

(8) M. Ikehara, H. Tada, and K. Muneyama, *ibid.*, **13**, 1140 (1965).

(9) Although Holmes reported[10] 1730–1750 cm^{-1} for the 8-keto function, all 8-keto purine ribosides showed 1720 cm^{-1} in our hands.

(10) R. E. Holmes and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 1772 (1965).

(11) In a previous study of the mesylation of 8-bromoguanosine[8] with 3 equiv of mesyl chloride using anhydrous pyridine purified by the usual procedure, dimesylguanosine was the main product. Part of the mesyl chloride may be deactivated by the formation of a complex with the strong amine present in the solvent.

(12) J. F. Codington, R. Fecher, and J. J. Fox, *ibid.*, **82**, 2794 (1960).

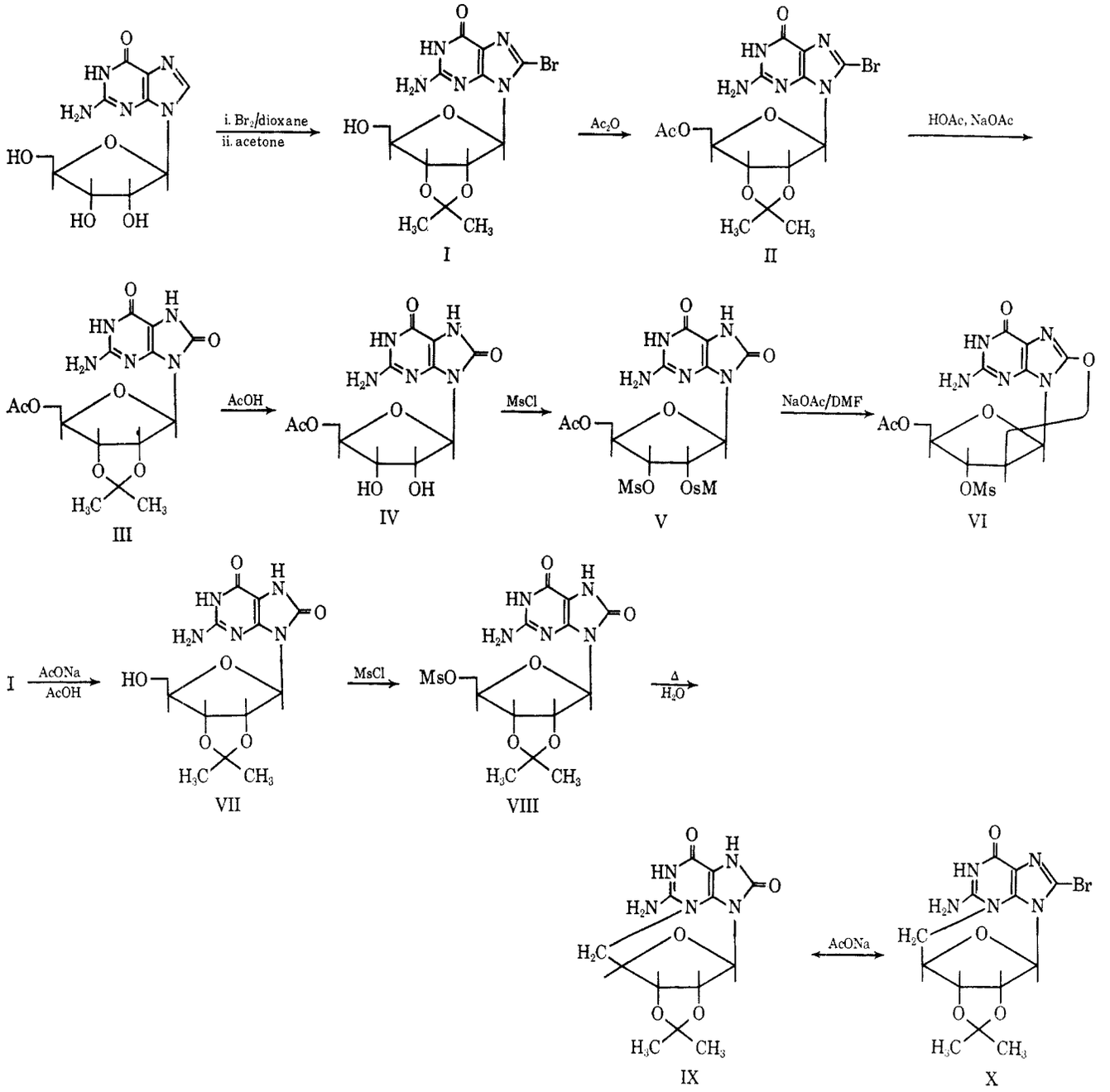
(13) M. Ikehara and K. Muneyama, *Chem. Pharm. Bull.*, **14**, 46 (1966).

(14) M. Ikehara, H. Tada, and M. Kaneko, unpublished results.

(15) N. C. Yung and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 3060 (1961).

(16) C. B. Reese and D. R. Trentham, *Tetrahedron Letters*, 2495 (1965).

SCHEME I



an 8,2′-*O* cyclo linkage was formed in guanosine as reported in adenosine series.[6]

Considering the formation of 8,2′-*O* cyclo linkage thus achieved, our attention has been drawn to the investigation of the 8,5′-*O* cyclization. For this purpose compound I was treated with acetic acid–sodium acetate to introduce the hydroxy function and afford 2′,3′-*O*-isopropylidene-8-oxyguanosine (VII). Reaction with 1 equiv of mesyl chloride with VII gave 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-8-oxyguanosine (VIII) as expected. The structure of VIII was confirmed by the elemental analyses and optical properties. When compound VIII was treated under cyclization conditions, there were obtained various types of cyclization products. Since, there are possibilities of forming 8,5′-, 5′,N^3-, and 5′,N^2-cyclonucleosides, the reaction mixture was analyzed by paper chromatography and optical properties. A typical example of the reaction was as follows. When compound VIII was refluxed with triethylamine in tetrahydrofuran for 1 hr, ultraviolet absorption changed from $\lambda_{max}^{H^+}$ 247 and 294 mμ to 256 and 288 mμ. The resulting compound IX had similar ultraviolet absorption properties to those observed in the heating of compound VII in water and not to those reported for 8-methoxyguanosine.[13] Since this reaction product has no mesyl group and still has the 8-keto group, the position of the cyclization can not be assigned to 8,5′, but to the N^3,5′ position. An analogous reaction of 2′,3′,5′-tri-*O*-mesyluridine to give three uracil pentofuranosides by the refluxing in water[17] and the cyclization of 2′,3′-*O*-isopropylidene-5′-*O*-tosylguanosine to form N^3,5′-cycloguanosine[18] also supported this reaction. The structure of compound IX was further confirmed by the reaction of

(17) J. F. Codington, R. Fecher, and J. J. Fox, *J. Org. Chem.*, **27**, 163 (1962).

(18) R. W. Chambers, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **79**, 3747 (1957).

N^3,5′-cyclo-8-bromoguanosine[19] with sodium acetate in acetic acid. In this case a product having similar ultraviolet absorption properties to IX was obtained.

Considering this evidence, reaction of 5′-*O*-mesyl-8-oxyguanosine seems to proceed with a fast cyclization of 5′ to N^3 instead of to the 8-hydroxyl to form the 8,5′-*O*-cyclonucleoside. This result is consistent with observations on the course of *S* cyclization in guanosine.

Experimental Section[20]

Paper Chromatography.—The following solvents were used: A, water adjusted at pH 10 with ammonia; B, 1-butanol–water, 86:14; C, 2-propanol–ammonia–water, 7:1:2. R_f (A) stands for the value on the paper chromatography performed in solvent A. Toyo filter paper No. 51 A was used.

2′,3′-*O*-Isopropylidene-8-bromoguanosine.—To warm (50–60°) methoxyethanol (600 ml) was added portionwise guanosine (5.66 g, well dried over phosphorus pentoxide at 50° and 2-mm pressure) to form a suspension. After stirring for 1 hr, the solution became almost clear. Calcium carbonate (12 g) was added and the mixture was allowed to cool to 30–38°. To this solution was added dropwise a dioxane (50 ml) solution of bromine (1.6 ml) during 1–2 hr. Warming (30–38°) was continued overnight with stirring. After cooling for 2–3 hr, precipitated calcium carbonate was removed by filtration. To the filtrate, acetone (200 ml) and dimethoxypropane (30 ml) were added, and the mixture was kept at room temperature overnight. After the addition of triethylamine (20 ml), the mixture was kept further for 1 day at room temperature. Insoluble material was removed by filtration and the filtrate was evaporated to a small volume (*ca.* 100 ml). Ether (100 ml) was added to cause a precipitate, which was collected by filtration and washed with ether and then water. Recrystallization from water gave a crystalline material in the yield of *ca.* 60%. *Anal.* Calcd for $C_{13}H_{16}N_5O_5Br$: C, 38.81; H, 3.98; N, 17.41. Found: C, 39.02; H, 4.05; N, 17.11. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 14,000), $\lambda_{max}^{H_2O}$ 263 mμ (ε 17,000), $\lambda_{max}^{pH\ 13}$ 272 mμ (ε 13,600). Paper chromatography showed R_f (A) 0.66, R_f (B) 0.73.

2′,3′-*O*-Isopropylidene-5′-*O*-acetyl-8-bromoguanosine.—2′,3′-*O*-Isopropylidene-8-bromoguanosine (1.2 g) was dissolved in 50 ml of pyridine, followed by the addition of 1.5 ml of acetic anhydride. The mixture was kept at room temperature overnight. Ethanol (20 ml) was added and the whole was kept at room temperature for an additional 3 hr. The solvent was evaporated *in vacuo* to afford a glass, which was crystallized from 30–40% aqueous ethanol (yield 70%). *Anal.* Calcd for $C_{15}H_{18}N_5O_6Br$: C, 40.54; H, 4.05; N, 15.77. Found: C, 40.24; H, 4.38; N, 15.96. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 16,000), $\lambda_{max}^{H_2O}$ 263 mμ (ε 15,400), $\lambda_{max}^{pH\ 13}$ 272 mμ (ε 13,000). The infrared spectrum showed ν_{max}^{Nujol} 1736 cm^{-1} (ester CO). Paper chromatography showed R_f (A) 0.51, R_f (B) 0.73.

2′,3′-*O*-Isopropylidene-5′-*O*-acetyl-8-oxyguanosine.—Freshly fused sodium acetate (3.3 g) was dissolved in 100 ml of glacial acetic acid with a slight warming. The clear solution was allowed to cool to below 20°. Isopropylideneacetyl-8-bromoguanosine (1.8 g) was suspended uniformly in this solution and the flask was immersed in an oil bath previously heated to 130–140°. The flask was shaken until the refluxing began. After 2-hr reaction, the solvent was removed by distillation *in vacuo*. Addition of 20 ml of ethanol and evaporation removed the residual acetic acid. This procedure was repeated three times until the odor of the acetic acid was totally removed. Finally, 120 ml of ethyl acetate was added and the mixture was refluxed for 2 hr in order to extract the product. Solid material was filtered while hot. The extraction was repeated three times; the extracts were combined and evaporated *in vacuo*. A hard oil (3.0 g) solidified after prolonged storage. Recrystallization from water gave a crystalline powder. *Anal.* Calcd for $C_{15}H_{19}O_7N_5 \cdot 1.5H_2O$: C, 46.15; N, 17.95. Found: C, 46.25; H, 5.23; N, 17.59. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 13,200), 294 (10,700); $\lambda_{max}^{H_2O}$ 247 mμ (ε 12,700), 274 (10,700); $\lambda_{max}^{pH\ 13}$ 257 mμ (ε 11,100), 278 (10,500). Paper chromatography showed R_f (A) 0.77, R_f (B) 0.75.

5′-*O*-Acetyl-8-oxyguanosine.—2′,3′-*O*-Isopropylidene-5′-*O*-acetyl-8-oxyguanosine (3.0 g) was dissolved in 33% acetic acid (40 ml) and the mixture was refluxed for 1–1.5 hr. After the solvent was removed *in vacuo*, the residue was recrystallized from water to afford a crystalline material. Yield calculated from isopropylideneacetylbromoguanosine was 38%. *Anal.* Calcd for $C_{12}H_{15}O_7N_5$: C, 42.23; H, 4.40; N, 20.53. Found: C, 42.18; N, 4.41; N, 20.58. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 248 mμ (ε 12,000), 294 (9100); $\lambda_{max}^{H_2O}$ 248 mμ (ε 12,200), 294 (9700); $\lambda_{max}^{pH\ 13}$ 257 mμ (ε 11,100), 278 (9900). The infrared spectrum showed ν_{max}^{Nujol} 1720 cm^{-1} (8-CO). Paper chromatography showed R_f (A) 0.76, R_f (B) 0.28. These spots were revealed by metaperiodatebenzidine spray.[21]

2′,3′-Di-*O*-mesyl-5′-*O*-acetyl-8-oxyguanosine.—5′-*O*-Acetyl-8-oxyguanosine (341 mg) was dissolved in 150 ml of dry pyridine (distilled from tosyl chloride and stored over molecular sieve), followed by the addition of a dry pyridine (20 ml) solution of mesyl chloride (0.17 ml) with cooling by ice–salt bath. The dropwise addition of mesyl chloride took 30–60 min. After this solution was kept at this temperature for 2 hr, the flask was stored in a refrigerator for 7 days and then at room temperature for 3 days. The solvent was completely removed by the distillation in the reduced pressure with the repeated addition of ethanol. The residue was recrystallized from ethanol to afford a solid (yield 30%). *Anal.* Calcd for $C_{14}H_{19}O_{11}N_5S_2 \cdot 1.5C_2H_6O$ (as containing 1.5 moles of ethanol): C, 34.61; H, 4.24; N, 13.46. Found: C, 34.51; H, 4.02; N, 13.01. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 245 mμ (ε 13,100), 295 (9500); $\lambda_{max}^{H_2O}$ 254 mμ (ε 12,300), 295 (10,000); $\lambda_{max}^{pH\ 13}$ 257 mμ (ε 12,700), 280 (10,100). The infrared absorption spectrum showed ν_{max}^{Nujol} 1720 (8-CO), 1170 cm^{-1} (RSOO). Paper chromatography showed R_f (C) 0.57.

8,2′-Cyclo-3′-mesyl-5′-*O*-acetylguanosine.—To freshly distilled dimethylformamide (30 ml) were added dimesylacetyl-8-oxyguanosine (100 mg) and sodium acetate (82 mg). The flask was immersed in an oil bath, which was previously heated to 90–100°, with stirring. Heating was continued for 4 hr. The solvent was removed by vacuum distillation and the residue was washed with a small amount of water to remove sodium acetate. Recrystallization from water gave a solid material (yield 30%). *Anal.* Calcd for $C_{13}H_{15}O_{18}N_5S \cdot 1.5H_2O$: C, 38.05; H, 3.90; N, 17.09. Found: C, 38.14; H, 3.84; N, 17.14. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 13,900), 286 (8600); $\lambda_{max}^{H_2O}$ 247 mμ (ε 14,100), 286 (8900), 251 (11,800), 269 (sh) (9300). The infrared spectrum showed no absorption band at ν_{max} 1720 cm^{-1} (8-CO). The nmr spectrum showed τ 6.53 (H_1, $J_{H1'-H2'}$ = 5.16 cps) (taken in dimethyl sulfoxide containing 1% D_2O).

2′,3′-*O*-Isopropylidene-5′-*O*-mesyl-8-oxyguanosine.—2′,3′-*O*-Isopropylidene-8 bromoguanosine (2.01 g, 5 mmoles) was dissolved in glacial acetic acid (150 ml) containing sodium acetate (4.1 g, 80 mmoles). After the mixture was refluxed for 1 hr, the solvent was removed *in vacuo*. The traces of acetic acid were distilled off by the repeated addition of ethanol. 2′,3′-*O*-Isopropylidene-8-oxyguanosine was obtained as an amorphous powder (yield 42%). Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 10,400), 294 (7500); $\lambda_{max}^{H_2O}$ 247 mμ (ε 12,900), 294 (8100); $\lambda_{max}^{pH\ 13}$ 258 mμ (ε 9000), 278 (8000). Paper chromatography showed R_f (A) 0.70, R_f (B) 0.55 accompanied by a thin spot of R_f (B) 0.71. The latter spot seems to be the 5′-*O*-acetyl derivative.[22] Ammoniacal treatment of this mixture remove the spot having R_f (B) 0.71.

2′,3′-*O*-Isopropylidene-8-oxyguanosine (680 mg, 2 mmoles), thus obtained, was dissolved in anhydrous pyridine, then treated with mesyl chloride (252 mg, 2.2 mmoles) with the cooling in an ice–salt bath. The reaction mixture was kept for 3 days at room temperature with exclusion of moisture. The pyridine solution was poured into ice–water and extracted with chloroform, and the chloroform layer was washed with sodium bicarbonate solution and finally with water. Evaporation of the chloroform solution *in vacuo* gave a gummy residue, which was crystallized from a water–ethanol mixture. The yield calculated from 2′,3′-*O*-isopropylidene-8-bromoguanosine was around 20%. *Anal.* Calcd for $C_{14}H_{19}O_8S \cdot H_2O$: C, 38.62; H, 4.83; N, 16.10. Found:

(19) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 3042 (1967).

(20) Ultraviolet absorption spectra were taken with Hitachi EPS-2U automatic recording spectrophotometer, infrared absorption spectra were taken with JASCO DS-301 spectrophotometer, and nmr spectra were taken with Hitachi H-60 spectrometer operated at 60 Mc using tetramethylsilane as internal standard. All melting points measured were above 200°.

(21) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

(22) In another experiment, in which refluxing was extended for 3 hr, the 5-′acetyl derivative was isolated and characterized (M. Ikehara and K. Murao, unpublished experiment).

C, 38.26; H, 4.38; N, 15.64. Ultraviolet absorption properties were $\lambda_{max}^{pH\ 1}$ 247 mμ (ε 13,800), 294 (13,200); $\lambda_{max}^{H_2O}$ 247 mμ (ε 13,100), 294 (12,400); $\lambda_{max}^{pH\ 13}$ 258 mμ (ε 11,100), 278 (10,700). The infrared absorption spectrum showed ν_{max}^{Nujol} 1170 cm^{-1} (RSO_2O). Paper chromatography showed R_f (B) 0.24, R_f (C) 0.34.

Attempted Cyclization of 2′,3′-*O*-Isopropylidene-5′-*O*-mesyl-8-oxyguanosine.—A small amount (*ca.* 5 mg) of 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-8-oxyguanosine was heated with the following reagents: (i) sodium acetate in dimethylformamide (or Methyl Cellosolve) at 100–110° for 1 hr; (ii) sodium acetate in dimethylformamide + acetic anhydride at 120–130° for 10 hr; (iii) triethylamine in tetrahydrofuran, refluxing for 1 hr; (iv) refluxing for 4 hr in tetrahydrofuran; (v) refluxing for 12 hr in water. In all these cases ultraviolet absorption of an aliquot withdrawn from the reaction mixture showed $\lambda_{max}^{H^+}$ 252–258, 287–290 mμ; $\lambda_{max}^{OH^-}$ 256–258 (sh), 298–300 mμ. Paper chromatography showed R_f (A) 0.66, R_f (B) 0.08. In the reaction in water (v) the pH of the reaction mixture became strongly acidic which may be caused by the liberated methylsulfonic acid.

N^3,5′-Cyclo-2′,3′-*O*-isopropylidene-8-oxyguanosine.—N^3,5′-Anhydro-2′,3′-*O*-isopropylidene-8-bromoguanosine[17] (4 mg) was refluxed with sodium acetate (8 mg) in acetic acid (10 ml) for 1 hr. Acetic acid was removed by distillation *in vacuo* and the residue was washed with water to remove sodium acetate. Solid material, thus obtained, showed the following ultraviolet absorption properties: $\lambda_{max}^{H^+}$ 251, 290 mμ; $\lambda_{max}^{OH^-}$ 258 (sh), 300 mμ. Paper chromatography showed R_f (A) 0.66, R_f (B) 0.08. These properties were well coincided with those observed in the above cyclization reactions.

Registry No.—I, 13591-82-7; II, 13591-83-8; III, 13591-84-9; IV, 13591-85-0; V, 13573-35-8; VI, 13591-86-1; VII, 13565-77-0; VIII, 13565-78-1; IX, 13591-87-2.

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Studies of Nucleosides and Nucleotides. XXXVI.[1] Purine Cyclonucleosides. 6.[2] Further Investigation on the Formation of 8,5′-*S*-Cyclonucleoside from Guanosine[3]

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2′,3′-*O*-Isopropylidene-5′-*O*-mesyl-8-bromoguanosine (II) was converted into 8,5′-anhydro-2′,3′-*O*-isopropylidene-8-mercaptoguanosine (III) *via* the 5′-*O*-mesyl derivative. The structure of III was elucidated by the desulfurization to afford 5′-deoxyguanosine, followed by the acid-catalyzed removal of the isopropylidene group. Another cyclonucleoside having the 5′,N^3-anhydro structure was obtained from compound II.

Recently, the synthesis of cyclonucleosides of purines have been reported[4–6] from our laboratory. Among these purine cyclonucleosides, 8,2′-*S*- and 8,2′-*O*- as well as 8,3′-*S*-cyclonucleosides in the adenosine series were investigated extensively as to their chemical and physical properties. Although an attempt to form an 8,5′-cyclonucleoside of adenosine failed because of a rapid cyclization to the N^3 position, a nucleoside having an 8,5′-*S* cyclo linkage could be synthesized in guanosine.[7] This fact indicated that in guanosine the cyclization to 8,5′-cyclonucleoside preceded N^3,5′ cyclization, presumably because of its lower pK value of base moiety than is the case for adenosine.[8] However, in this instance 2′,5′-di-*O*-mesyl-8-bromoguanosine was chosen as the starting material and the resulting cyclonucleoside has a mesyl group on 2′ position, which could not easily be removed. We have, therefore, reinvestigated the formation of the 8,5′-*S* cyclo linkage in 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-8-bromoguanosine and, from the resulting cyclonucleoside, 5′-deoxyguanosine could be obtained by the desulfurization with Raney nickel. In the course of this study, a cyclization by product, N^3,5′-cyclo-8-bromoguanosine, was obtained.

2′,3′-*O*-Isopropylidene-8-bromoguanosine[10,11] (I) was mesylated with 1.2 equiv of mesyl chloride in pyridine to afford the 5′-*O*-mesyl derivative (II) (Scheme I). Although ultraviolet absorption properties of compound II showed a slight shift of the absorption maxima from those of 8-bromoguanosine,[7,12] a similar change observed for 2′,5′-di-*O*-mesyl-8-bromoguanosine[7] suggested that the mesylation had occurred only on the furanose moiety. An infrared absorption band at 1170 cm^{-1} also suggested this view. Since the elemental analytical data confirmed the monomesylation, the structure of compound II was established at 2′,3′-*O*-isopropylidene-5′-*O*-mesyl-8-bromoguanosine.

The cyclization reaction was carried out by refluxing with thiourea as reported previously.[7] When compound II was refluxed in dioxane or tetrahydrofuran[13] in the presence of thiourea, a compound (III) having ultraviolet absorption properties similar to those reported for 8-methylmercaptoguanosine[12,15] was obtained. From the previous studies of the purine cyclonucleosides,[6,7] the similarity in ultraviolet absorption properties of compound III with 8-methylmercaptoguanosine was as expected. Although the efforts to crystallize compound III failed, a glass obtained by the vacuum evaporation of the solvent showed an elemental

(1) Part XXXV: M. Ikehara, H. Tada, and M. Kaneko, in preparation.

(2) Part 5 of this series, same as above.

(3) This work has been presented at the Hokkaido Regional Meeting of Pharmaceutical Society of Japan, 1966.

(4) M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963); **87**, 606 (1965).

(5) M. Ikehara and H. Tada, *Chem. Pharm. Bull.*, **15**, 94 (1967).

(6) M. Ikehara, H. Tada, J. Muneyama, and M. Kaneko, *J. Am. Chem. Soc.*, **88**, 3165 (1966).

(7) M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.*, **13**, 639 (1965).

(8) N^6 acetylation of adenosine inhibited the N^3,5′ cyclization of 5′-*O*-tosyladenosine.[9]

(9) W. Jahn, *Chem. Ber.*, **98**, 1705 (1965).

(10) M. Ikehara, H. Tada, and K. Muneyama, *Chem. Pharm. Bull.*, **13**, 1140 (1965).

(11) M. Ikehara and K. Muneyama, *J. Org. Chem.*, **32**, 0000 (1967).

(12) R. E. Holmes and R. K. Holmes, *J. Am. Chem. Soc.*, **86**, 1242 (1964).

(13) Since these solvents extremely enhanced the reaction, some interaction[14] with bromoguanine moiety could be assumed.

(14) R. A. Vitali, E. S. Inamine, and T. A. Jacob, *Arch. Biochem. Biophys.*, **112**, 313 (1965).

(15) M. Ikehara and K. Muneyama, *Chem. Pharm. Bull.*, **14**, 46 (1966).