[Chem. Pharm. Bull. 16(8)1466—1471(1968)]

UDC 547.823.04

Studies on Prototropic Tautomerism in Nitrogen Heterocyclic Compounds. I. The Mannich Reaction of 2(1*H*)-Pyridone and 3-Hydroxy-2(1*H*)-pyridone[1]

Akitada Nakamura and Shozo Kamiya

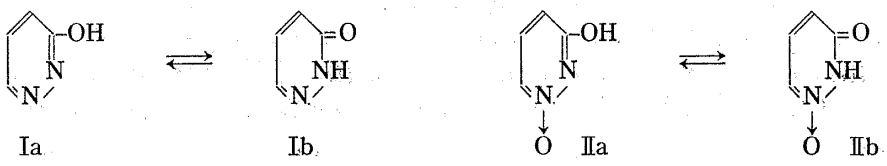
National Institute of Hygienic Sciences[2]

(Received August 26, 1967)

The Mannich reaction of 3-hydroxy-2(1*H*)-pyridone, in which both a phenolic OH and a lactam NH are present in a molecule, was examined, and 3-hydroxy-6-piperidinomethyl-2 (1*H*)-pyridone (IXa) and 3-hydroxy-4,6-bis(piperidinomethyl)-2(1*H*)-pyridone (X) were obtained in 82 and 5% yields, respectively.

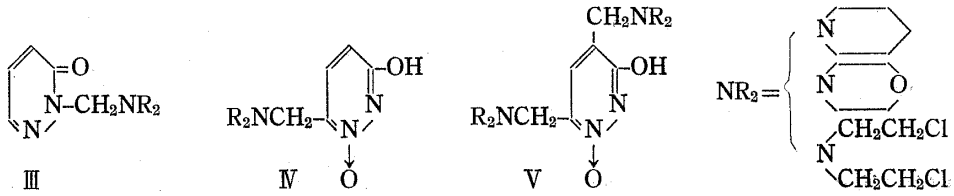
The reaction of IXa with the cyclohexanone pyrrolidine enamine gave 4a,7-dihydroxy-1,2,3,4,4a,10a-hexahydrobenzo[*b*]indolizin-6(10*H*)-one (XVI) in 82% yield.

It is well known that 3-pyridazinol (Ia) exists as the alternative lactam form, 3(2*H*)-pyridazinone (Ib) in both solid and solution. On the other hand, 3-pyridazinol 1-oxide (IIa) can tautomerize to the lactam form, 3(2*H*)-pyridazinone 1-oxide (IIb), but the enol form (IIa) is predominant in both solid and solution.



Ia Ib IIa IIb

In the previous paper,[3] it was shown that the Mannich reaction of Ib using formalin and a secondary amine such as piperidine, morpholine or 2,2'-dichlorodiethylamine gave an N-Mannich base (III). Contrarily, the same reaction of IIa produced a C-Mannich base[4] as 6-alkylaminomethyl-3-pyridazinol 1-oxide (IV), and treatment of IIa with excess amounts of the reagents also gave a 4,6-disubstituted derivative (V).



III IV V

This fact reveals that the hydroxyl group of the 3-position in IIa is practically phenolic, though it is present at the *ortho* position of the 2-nitrogen.

These behaviors of Ib and IIa toward the Mannich reaction well agree with those that can be presumed from the structures obtained by various physical methods. Consequently, the Mannich reaction seems to be a significant chemical means for the studies of prototropic tautomerism in the oxo-derivatives of nitrogen heterocycles.

1) A part of this work was presented at the 24th Annual Meeting of the Pharmaceutical Society of Japan at Kyoto, April, 1967.
2) Location: *Tamagawayoga, Setagaya, Tokyo.*
3) S. Kamiya, A. Nakamura, T. Itai, K. Koshinuma, and G. Okusa, *Yakugaku Zasshi*, **86**, 1099 (1966).
4) G. Okusa, S. Kamiya, and T. Itai, *Chem. Pharm. Bull.* (Tokyo), **15**, 1172 (1967).

It is, therefore, of interest to study the Mannich reaction of 3–hydroxy–2(1*H*)–pyridone (VIIIa), in which both a lactam NH and a phenolic OH are present in a molecule, as an extension of our studies on the Mannich reaction of the oxo–derivatives of nitrogen heterocycles.

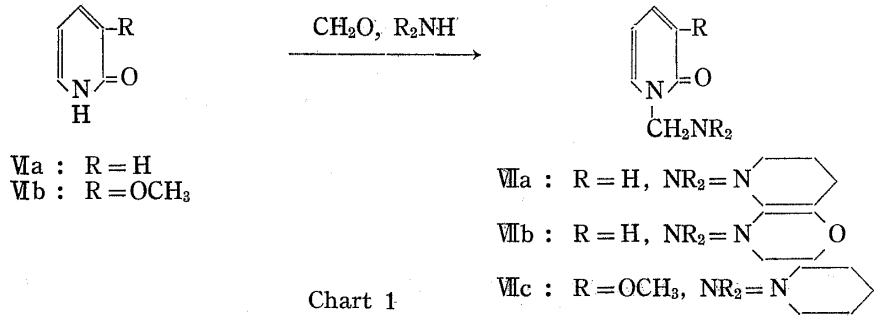
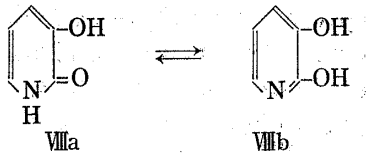


Chart 1

The Mannich reaction of 2(1*H*)–pyridones which have a lactam NH, was examined in connection with VIIIa at first. Treatment of 2(1*H*)–pyridone (VIa) or 3–methoxy–2(1*H*)–pyridone (VIb) with an equimolar mixture of paraformaldehyde and a cyclic secondary amine such as piperidine or morpholine in a sealed tube gave the corresponding Mannich bases. Their infrared spectra show the lactam CO at 1650—1660 cm^{-1} and lack in the absorptions due to the NH which are observable in those of VIa and VIb. In addition, they decomposed to liberate formalin and VI in boiling water. These facts indicate that they are all N–Mannich bases, 1–piperidinomethyl–2(1*H*)–pyridone (VIIa), 1–morpholinomethyl–2(1*H*)–pyridone (VIIb) and 1–piperidinomethyl–3–methoxy–2(1*H*)–pyridone (VIIc), as shown in Chart 1.



3–Hydroxy–2(1*H*)–pyridone (VIIIa) can tautomerize to 2,3–dihydroxypyridine (VIIIb) by prototropy, but contribution of the lactam form (VIIIa) is considered to be predominant on the basis of its infrared spectrum in a potassium bromide disk, showing the presence of a hydroxy group at 3270 cm^{-1}, a lactam NH at 3150 cm^{-1} and a lactam CO at 1660 cm^{-1}. Predominance of the lactam form in this prototropic tautomerism is also supported by close similarity in the ultraviolet spectra of VIIIa, λ_{max}^{EtOH} mμ (ε): 240 (2810), 299 (4690) and 3–methoxy–2(1*H*)–pyridone (VIb), λ_{max}^{EtOH} mμ (ε): 239 (7370), 295 (8640).

When VIIIa was heated with an equimolar mixture of paraformaldehyde and piperidine in ethanol at 100°, two kinds of products, A (mp 215° decomp.) as a major and B (mp 184—185° decomp.) as a minor, were isolated from the reaction mixture. The analytical data fit the mono–Mannich base for A and di–Mannich base for B. The reaction of VIIIa with paraformaldehyde and piperidine in a ratio of 1:2:4, respectively, gave an 80% yield of the di–Mannich base.

The infrared spectra of the mono– and di–Mannich bases show the presence of hydroxy groups at 3260—3280 cm^{-1}, lactam NH at 3105—3100 cm^{-1} and lactam CO at 1650 cm^{-1}. Then, the nuclear magnetic resonance (NMR) spectra of these Mannich bases were measured to determine the alkylaminomethylated positions.

The NMR studies[5] of various methyl substituted 2(1*H*)–pyridones in deuterochloroform have shown that the signals of these ring protons appear at H^4: 2.7—2.8 τ, H^5: 3.8—4.2 τ, H^6: 2.6—3.0 τ and H^3: 3.5—3.8 τ. In the NMR spectrum of the di–Mannich base in deuterochloroform, only an aromatic proton is observable at 4.27 τ as a singlet that is clearly assigned as H^5–proton from the parameters mentioned above. Consequently, the di–Mannich base is 3–hydroxy–4,6–bis(piperidinomethyl)–2(1*H*)–pyridone (X) as shown in Chart 2. In that of the mono–Mannich base, a pair of doublet is observable at 3.84 τ (J=7.2 cps) and 2.28 τ

5) C.L. Bell, R.S. Egan, and L. Bauer, *J. Heterocyclic Chem.*, **2**, 420 (1965).

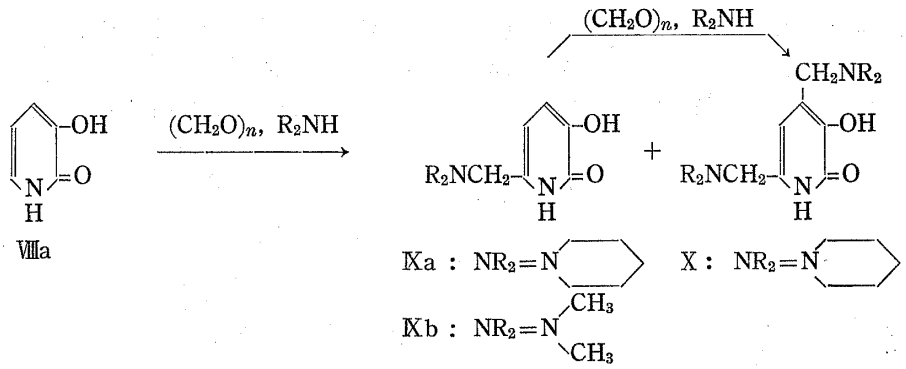
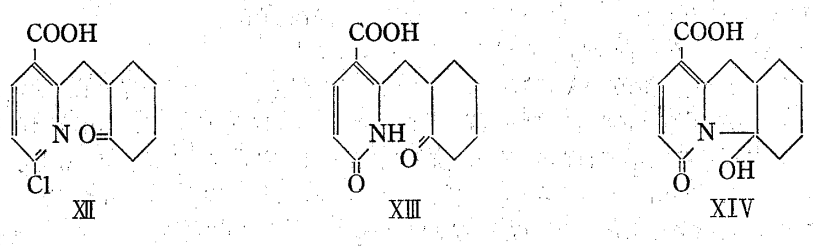


Chart 2

(J=7.2 cps), and the values of spin–spin coupling constant are reasonable for *ortho* coupling of the ring protons. The doublet at 3.84 τ is reasonable to assign as H^5–proton, but the doublet at 2.82 τ is not able to assign definitely whether it belongs to H^6–proton or H^4–proton because of their close values.

The condensation reaction of the mono–Mannich base with the cyclohexanone enamine was, then, tried in order to determine the alkylaminomethylated position definitely.

Ramirez and Paul[6] reported that the compound obtained from the alkaline hydrolysis of 2–(2′–oxocyclohexyl)methyl–6–chloronicotinic acid (XII) was not 1,6–dihydro–2–(2′–oxocyclohexyl)methyl–6–oxonicotinic acid (XIII), but 4a–hydroxy–6–oxo–1,2,3,4,4a,5,6,10a–octahydrobenzo[*b*]indolizin–9–carboxylic acid (XIV), the ring–tautomer of XIII, since it exhibited these bands at 3380 cm^{-1} (OH), 1690 cm^{-1} (COOH) and 1620 cm^{-1} (lactam CO) but no band due to a six–membered ketone (1715—1720 cm^{-1}).



If the alkylaminomethylated position in the mono–Mannich base derived from VIIIa is the 6–position, such a tricyclic compound as XIV must be obtained by the condensation reaction of IXa with the cyclohexanone enamine.

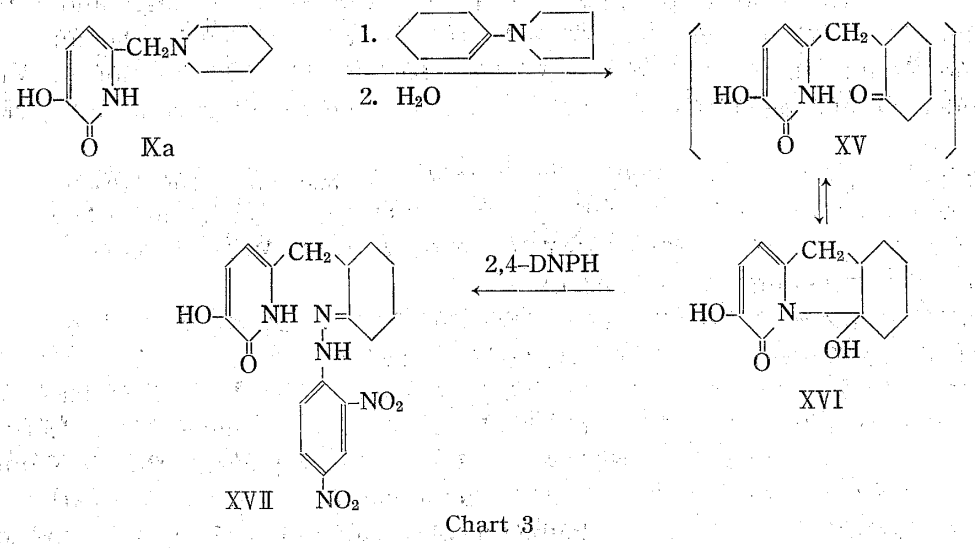


Chart 3

6) F. Ramirez and A.P. Paul, *J. Am. Chem. Soc.*, 77, 3337 (1955).

Treatment of IXa with the cyclohexanone pyrrolidine enamine at the boiling temperature in a dioxane medium followed by hydrolysis produced a condensation product in 82% yield. As shown in Fig. 1–b, its infrared spectrum in a potassium bromide disk lacks in the absorptions due to a six-membered ketone (1715—1720 cm^{-1}) and to a lactam NH which is clearly observable at 3105 cm^{-1} in that of IXa (Fig. 1–a). In order to obtain an additional spectral evidence for absence of the lactam NH in the condensation product (XVI), IXa and XVI were both deuterated with deuterium oxide. As shown in Fig. 1–a, the infrared spectrum of the deuterated IXa shows two new bands at 2426 and 2226 cm^{-1}.

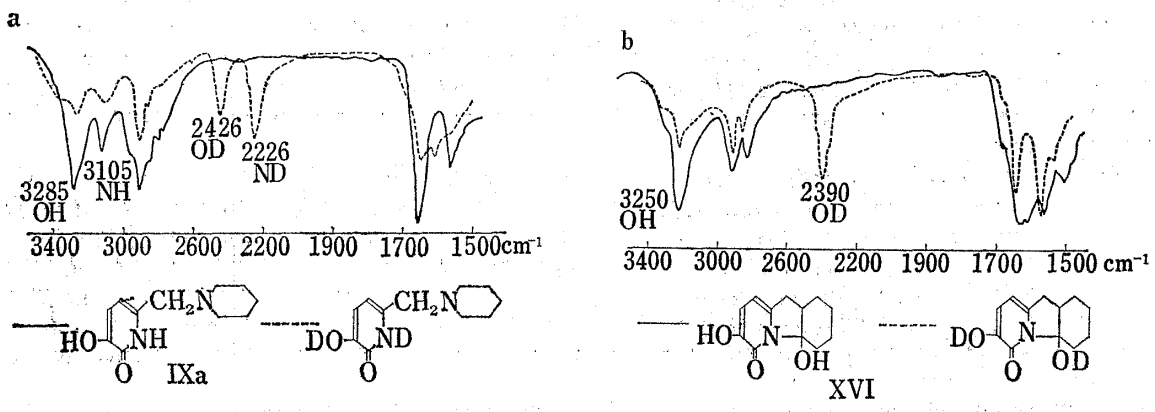


Fig. 1. The Infrared Spectra of 3–Hydroxy–6–piperidinomethyl–2(1*H*)–pyridone (IXa), 7,4a–Dihydroxy–1,2,3,4,4a,10a–hexahydrobenzo[*b*]indolizin–6(10*H*)–one (XVI) and Their Deuterated Compounds at 3400—1500 cm^{-1} (in KBr)

Since the νND absorption of 2(1*H*)–pyridone (VIa) appears at 2285 cm^{-1}, the band at 2226 cm^{-1} in that of the deuterated IXa (νNH/ND=1.39) is attributable to νND, and the band at 2426 cm^{-1} (νOH/OD=1.35) is, therefore, assigned as νOD. On the other hand, the infrared spectrum of the deuterated XVI shows a new strong band at 2390 cm^{-1} (νOH/OD =1.37) that is reasonable to assign as νOD, and no νND band is observable. In this case, the absorption of the OD in the pyridone nuclei overlaps with that of the aliphatic tertiary OD, showing a strong OD band.

Consequently, the structure of XVI as a tricyclic form, 4a,7–dihydroxy–1,2,3,4,4a,10a–hexahydrobenzo[*b*]indolizin–6(10*H*)–one, gave a chemical proof that an alkylaminomethyl group was introduced into the 6–position adjacent to the lactam NH in VIIIa.

When XVI reacted with 2,4–dinitrophenylhydrazine, a 2,4–dinitrophenylhydrazone was obtained. Its infared spectrum in nujol shows the presence of a lactam NH at 3080 cm^{-1} and a hydrazone NH at 3300 cm^{-1}, and its ultraviolet absorption maximum (365 mμ) is the same with that of the 2,4–dinitrophenylhydrazone of cyclohexanone.[6] From these spectral data, this hydrazone should be that of the chain form (XV). The formation of XVII strongly suggests the presence of a ring–chain tautomerism between the chain form (XV) and the ring form (XVI) in solution. This assumption was substantiated by measuring its NMR spectrum. The more precise investigation on the prototropic tautomerism of this type using NMR spectroscopy, will be reported in the forthcoming paper.

The Mannich bases prepared in this work did not show bacteriostatic activities bellow concentration of 1000 μg/ml against *Escherichia coli*, *Staphylococcus aureus* and *Mycobacterium 607*. Other biological tests are under investigation, the results of which will be reported separately.

7) Purchased from the Aldrich Chemical Co.

Experimental[8]

1-Piperidinomethyl-2(1*H*)-pyridone (VIIa)——A typical experiment for the 1-alkylaminomethyl-2(1*H*)-pyridones is described with 1-piperidinomethyl-2(1*H*)-pyridone. To a mixture of 0.95 g (0.01 mole) of 2(1*H*)-pyridone, 1 ml (0.01 mole) of piperidine and 3 ml of ethanol, was added dropwise 1 ml of 37% formalin (0.01 mole). The reaction mixture was allowed to stand at room temperature for 3 hr, evaporated to dryness under reduced pressure, and the residue was dried in an evacuated desiccator. The residue was extracted with hot petroleum ether and the combined extracts were concentrated until the crystals began to separate. The mixture was allowed to stand overnight, the separated crystals were filtered, and washed with petroleum ether. Yield, 0.85 g (45%). Colorless needles (from ether), mp 66°. IR ν_{max}^{Nujol} cm^{-1}: 1660 (lactam CO). *Anal.* Calcd. for $C_{11}H_{16}ON_2 \cdot \frac{1}{2}H_2O$: C, 65.64; H, 8.51; N, 13.92. Found: C, 65.51; H, 8.62; N, 14.39.

1-Morpholinomethyl-2(1*H*)-pyridone (VIIb): Colorless needles, mp 79° (from pet. ether). Yield, 18%. *Anal.* Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.57; H, 7.08; N, 14.01.

1-Piperidinomethyl-3-methoxy-2(1*H*)-pyridone (VIIc): Colorless granules, mp 69—71° (from isopropyl ether). Yield, 48%. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2 \cdot \frac{1}{2}H_2O$: C, 62.31; H, 8.28; N, 12.11. Found: C, 63.09; H, 8.37; N, 12.42.

3-Methoxy-2(1*H*)-pyridone (VIb)——To an ice-cooled solution of 2.2 g (0.02 mole) of 3-hydroxy-2(1*H*)-pyridone[8] in a solution of 0.86 g of sodium hydroxide in 15 ml of water, was added dropwise 2.6 g (0.02 mole) of dimethyl sulfate with stirring. After stirring for 2 hr at room temperature, the reaction mixture was acidified with acetic acid, and extracted with six successive 100 ml portions of chloroform. The chloroform layer was dried over anhyd. sodium sulfate and evaporated to dryness. Yield, 1.95 g (76%). The product is recrystallized twice from chloroform to give colorless leaflets, mp 114—116°. IR ν_{max}^{Nujol} cm^{-1}: 3200—2400 (lactam NH), 1660 (lactam CO), 1250, 1010 (C–O–C). *Anal.* Calcd. for $C_6H_7O_2N$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.89; H, 5.73; N, 11.52.

3-Hydroxy-6-piperidinomethyl-2(1*H*)-pyridone (IXa) and 3-Hydroxy-4,6-bis(piperidinomethyl)-2(1*H*)pyridone (X)——A mixture of 1.11 g (0.01 mole) of 3-hydroxy-2(1*H*)-pyridone, 0.3 g (0.01 mole) of paraformaldehyde, 0.9 g (0.01 mole) of piperidine and 20 ml of methanol, was heated in a sealed tube at 100° for 2 hr, and the reaction mixture was let stand at room temperature overnight. The residue was treated with chloroform, filtered* and dried. 3-Hydroxy-6-piperidinomethyl-2(1*H*)-pyridone, 1.66 g (82%). Colorless needles (from chloroform), mp *ca.* 215° (decomp.). This compound did not show a distinct melting point. UV λ_{max}^{EtOH} $m\mu$ (ε): 244 (3450), 301 (5600). *Anal.* Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.31; H, 7.65; N, 13.90.

*The filtrate was evaporated to dryness and the residue was recrystallized from ethyl acetate to give colorless needles, mp 180—182° (decomp.), 3-hydorxy-4,6-bis(piperidinomethyl)-2(1*H*)-pyridone (X), 0.15 g (5%). Two repeated recrystallization from ethyl acetate gave an analytical sample, mp 184—185° (decomp). UV λ_{max}^{EtOH} $m\mu$ (ε): 248 (5100), 307 (8100). *Anal.* Calcd. for $C_{17}H_{27}O_2N_3$: C, 66.85; H, 8.91; N, 13.76. Found: C, 66.30; H, 8.62; N, 13.73.

Analogously, 3-hydroxy-6-dimethylaminomethyl-2(1*H*)-pyridone (IXb) was synthesized in 49% yield. Colorless needles (from chloroform), mp *ca.* 193° (decomp.). This compound also did not show a distinct melting point. *Anal.* Calcd. for $C_8H_{12}O_2N_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.09; H, 7.30; N, 16.62.

4a,7-Dihydroxy-1,2,3,4,4a,10a-hexahydrobenzo[*b*]indolizin-6(10*H*)-one (XVI)——A mixture of 4.0 g (0.04 mole) of cyclohexanone, 2.96 g (0.04 mole) of pyrrolidine and 50 ml of dehyd. benzene was refluxed in a flask attached to a Dean–Stork water separator for 3 hr, during which time 0.4 ml of water was collected. The reaction mixture was evaporated to dryness under reduced pressure. To the residue was added 4.2 g (0.02 mole) of 3-hydroxy-6-piperidinomethyl-2(1*H*)-pyridone (IXa) and 60 ml of dehyd. dioxane, the mixture was refluxed for 10 hr, and the reaction mixture was evaporated to dryness under reduced pressure. The residue was heated in a 50 ml of water at the boiling temperature for 2 hr, and the reaction mixture was evaporated to dryness under reduced pressure. The residue was treated with ethanol, and filtered. Yield, 3.75 g (82%), mp 225—226° (decomp.). The product was recrystallized from ethanol three times to give a colorless powder, mp 236—237° (decomp.). UV λ_{max}^{EtOH} $m\mu$ (ε): 244 (4900), 294 (7050). *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.98; H, 7.08; N, 6.31.

2,4-Dinitrophenylhydrazone (XVII): Yellow needles, mp 228—229° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 3300 (hydrazone NH), 3240 (OH), 3080 (lactam NH), 1645 (lactam CO). UV λ_{max}^{EtOH} $m\mu$: 365. *Anal.* Calcd. for $C_{18}H_{19}O_6N_5$: C, 53.86; H, 4.77; N, 17.46. Found: C, 53.93; H, 4.77; N, 17.47.

Preparation of Deuterated Compounds——Replacement of the hydrogens of NH and OH in these compounds was accomplished as follows. A sample was dissolved in an excess amount of deuterium oxide, and

8) All melting points are uncorrected. Infrared and ultraviolet spectra were measured on a JASCO Model-IR infrared spectrophotometer, and on a Hitachi Model EPS-2 ultraviolet spectrophotometer. NMR spectra were determined on a Varian HR-100 spectrophotometer.

the solution was evaporated under reduced pressure. This procedure was repeated three or four times. The residue was dried over potassium hydroxide in vaccum, and its infrared spectrum was measured in a potassium bromide disk.

Acknowledgement The authors are indebted to Dr. K. Koshinuma of this institute for bacteriostatic screening. They also thank Drs. M. Ishidate, I. Suzuki, S. Iwahara of this institute for their interests, and the National Institute of Radiological Sciences for NMR measuring.