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NOTE

# Synthesis and antibacterial activity of 1-*N*-[(*S*)-ω-amino-2-hydroxyalkyl] derivatives of dibekacin, 5-deoxydibekacin, 3′-deoxykanamycin A and gentamicin B

**Eijiro Umemura, Yukou Sakamoto, Yoshiaki Takahashi and Toshiaki Miyake**

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Aminoglycoside antibiotics are highly potent, broad-spectrum agents for the treatment of life-threatening infections. From 1971–1978, semisynthetic aminoglycosides such as dibekacin,[1] amikacin (AMK),[2] netilmicin,[3] isepamicin (**1d**)[4] and arbekacin (**1a**)[5] were developed. Among them, AMK, isepamicin and arbekacin have an (*S*)-ω-amino-2-hydroxyalkanoyl residue on the 1-amino group, making them more resistant to the action of aminoglycoside-modifying enzymes such as aminoglycoside acetyltransferase (AAC), aminoglycoside phosphotransferase (APH) and aminoglycoside adenylyltransferase (AAD). For example, arbekacin is stable against the bifunctional enzyme AAC(6′)-APH(2″) contained in methicillin-resistant *Staphylococcus aureus* and effective against almost all resistant bacteria that produce aminoglycoside-modifying enzymes.

For the aminoglycoside antibiotics with the 2-deoxystreptamine component, the hydrogen bonding interaction between the 1-amino group and U1495 of the bacterial 16S rRNA is known.[6] However, the N-1 atoms of 1-*N*-aminoalkanoyl compounds are no longer basic or ionizable, and the basic amino functions are located at the end of the side chains instead. Therefore, the hydrogen bonding of 1-*N*-aminoalkanoyl compounds may be weaker than that of 1-amino derivatives.

Richardson *et al.*[7] synthesized 1-*N*-aminoalkyl derivatives of kanamycin A by borane reduction of the corresponding 1-*N*-aminoalkanoyl derivatives and characterized their antibacterial activities. Among them, 1-*N*-[(*S*)-4-amino-2-hydroxybutyl]kanamycin A (butikacin), which is an AMK analog, showed excellent antibacterial activity similar to that of AMK and with a lower ototoxicity than that of AMK.[8]

In an effort to clarify the relationship between the recovery of basicity at the N-1 atom with the antibacterial activity and biological properties, the transformation of 1-*N*-aminoalkanoyl compounds of various aminoglycoside antibiotics to the corresponding 1-*N*-aminoalkyl analogs is of interest. We selected arbekacin (**1a**), 5-deoxyarbekacin[9] (**1b**), 3′-deoxyamikacin[10] (**1c**) and isepamicin (**1d**) for further study (Scheme 1). Compounds **1a–c** have superior antibacterial activity to AMK and **1d** is known to be less toxic than AMK.

The trifluoroacetate salts of each antibiotic were used to improve their solubilities because their respective free bases or inorganic salts were only minimally soluble in the reaction solvent tetrahydrofuran. First, arbekacin (**1a**) trifluoroacetate was reduced with diborane in tetrahydrofuran, and following treatment with aqueous sodium hydroxide, 1-*N*-[(*S*)-4-amino-2-hydroxybutyl]dibekacin (**2a**) was obtained in moderate yield after purification by column chromatography with ion-exchange resin. The above alkaline hydrolysis reaction converted the unreacted **1a** to the 1-amino derivative and facilitated the purification step. In the $^{1}$H NMR spectrum of **2a** in 25% $ND_3/D_2O$, the H-2‴ signal at 4.52 p.p.m. of **1a** shifted to 4.13 p.p.m. and the new signals for H-1‴ appeared at 2.88 and 3.16 p.p.m. In the $^{13}$C NMR spectrum, the C-1‴ signal at 177.0 p.p.m. of **1a** was shifted to 57.3 p.p.m., confirming the structure of **2a**.

Borane reductions for 5-deoxyarbekacin, 3′-deoxyamikacin and isepamicin were also carried out in a similar fashion to yield 1-*N*-[(*S*)-4-amino-2-hydroxybutyl]-5-deoxydibekacin (**2b**), 1-*N*-[(*S*)-4-amino-2-hydroxybutyl]-3′-deoxykanamycin A (**2c**) and 1-*N*-[(*S*)-3-amino-2-hydroxypropyl]gentamicin B (**2d**), respectively. A large portion of **1c** was recovered as starting material because of its poor solubility. As a result, the yield of **2c** was lower than those of the other compounds. Their structures were also confirmed by $^{1}$H NMR, $^{13}$C NMR and MS spectra as described for **2a**.

Table 1 shows the antibacterial activity of the resulting 1-*N*-aminoalkyl derivatives **2a–d** and their parent antibiotics **1a–d**. In contrast to AMK,[7] the kanamycin-type compounds **2a–c** were less

Institute of Microbial Chemistry (BIKAKEN), Kanagawa, Japan
Correspondence: Dr E Umemura, Institute of Microbial Chemistry (BIKAKEN), Hiyoshi, 3-34-17, Ida, Nakahara-ku, Kawasaki, Kanagawa 211-0035, Japan.
E-mail: umemurae@bikaken.or.jp
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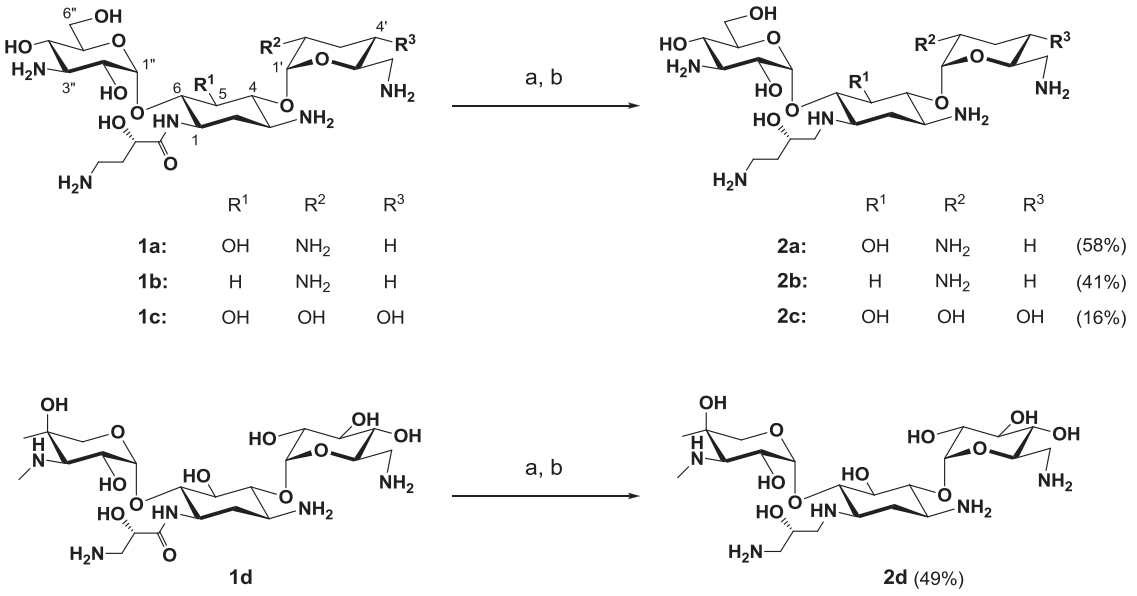


**Scheme 1** Synthesis of 1-*N*-[(*S*)-ω-amino-2-hydroxyalkyl] derivatives **2a**–**d**. Reagents and conditions: (a) diborane, trifluoroacetic acid, tetrahydrofuran, 50 °C, 6 h; (b) NaOH, $H_2O$, 100 °C, 1 h.

**Table 1** ***In vitro*** **antibacterial activities (MIC, μg ml$^{-1}$) of 1a–d and 2a–d**

| *Test organisms*[a] | *Characteristics* | ***1a*** | ***2a*** | ***1b*** | ***2b*** | ***1c*** | ***2c*** | ***1d*** | ***2d*** |
|---|---|---|---|---|---|---|---|---|---|
| *Staphylococcus aureus* 209PJC-1 | Sensitive | 0.12 | 0.5 | 0.12 | 0.25 | 0.25 | 0.25 | 1 | 0.25 |
| *Staphylococcus aureus* RN4220 | Sensitive | 1 | 4 | 1 | 2 | 2 | 4 | 4 | 4 |
| *Staphylococcus aureus* RN4220/pMS18 | APH(3′)-III | 1 | 4 | 1 | 2 | 2 | 4 | 16 | 8 |
| *Staphylococcus aureus* RN4220/pMS520 | AAD(4′)-I | 1 | 4 | 1 | 2 | 8 | 32 | 64 | >64 |
| *Staphylococcus aureus* MF490Cu | AAD(4′)-I | 2 | 8 | 4 | 4 | 32 | 32 | >64 | >64 |
| *Escherichia coli* JM109 | Sensitive | 0.5 | 1 | 0.5 | 1 | 0.5 | 1 | 0.5 | 0.5 |
| *Escherichia coli* JM109/pHSG298 | APH(3′)-III | 0.5 | 1 | 0.5 | 1 | 0.5 | 1 | 1 | 1 |
| *Pseudomonas aeruginosa* PAO1 | Sensitive | 2 | 4 | 1 | 1 | 2 | 2 | 4 | 2 |
| *Pseudomonas aeruginosa* PAO1/GN4925 | AAC(6′)-Ib | 2 | 4 | 1 | 8 | 2 | 16 | 4 | 4 |
| *Pseudomonas aeruginosa* GN3054 | AAC(3)-III | 4 | 8 | 2 | 4 | 4 | 8 | 8 | 8 |
| *Pseudomonas aeruginosa* PAO1/ML4847 | AAC(3)-III | 2 | 4 | 1 | 1 | 2 | 2 | 4 | 4 |
| *Pseudomonas aeruginosa* MSC17711 | AAC(6′)-Ib[b] | 8 | 16 | 4 | 64 | 8 | 32 | 16 | 16 |
| *Pseudomonas aeruginosa* MSC17707 | AAC(6′)-Iae[c] | 4 | 8 | 8 | >64 | 8 | >64 | >64 | >64 |

Abbreviations: AAC, aminoglycoside acetyltransferase; AAD, aminoglycoside adenylyltransferase; APH, aminoglycoside phosphotransferase.
[a]Agar dilution steak method (Mueller-Hinton agar, 17 h, 37 °C)
[b]Gentamicin-resistant strain.
[c]Amikacin-resistant strain.

active than the parent antibiotics **1a–c**. This indicated that the recovery of the basicity at the N-1 atom does not necessarily contribute to the improvement of the antibacterial activity in the kanamycin-type antibiotics. In contrast, the 1-*N*-aminoalkyl derivative **2d** of the gentamicin-type antibiotics was more active than the parent antibiotic **1d**.

In conclusion, we synthesized the 1-*N*-[(*S*)-ω-amino-2-hydroxyalkyl] derivatives of a variety of aminoglycoside antibiotics and evaluated their antibacterial activities. The superiority of the 1-*N*-aminoalkyl derivatives compared with the 1-*N*-aminoalkanoyl derivatives with respect to their antibacterial activities was not observed in the kanamycin-type antibiotics **2a–c**. However, antibacterial activity enhancement was shown for the gentamicin-type antibiotic **2d**. Further work into the effects of the 1-*N*-aminoalkyl modification on other types of aminoglycoside antibiotics is underway in our laboratory.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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