Tetrahedron Letters No.5, pp. 623–627, 1968. Pergamon Press. Printed in Great Britain.

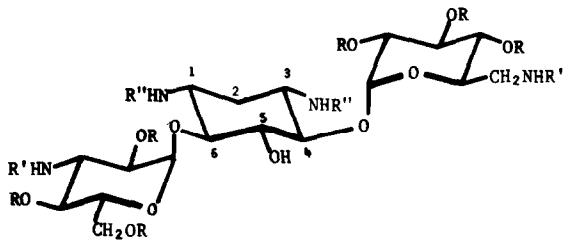
TOTAL SYNTHESIS OF KANAMYCIN-A

Minoru Nakajima, Akira Hasegawa, Norio Kurihara,
Hisao Shibata, Tamio Ueno and Daikichi Nishimura
Department of Agricultural Chemistry, Kyoto University, Kyoto, Japan

(Received in Japan 6 October 1967)

Kanamycin-A, discovered by Umezawa and his coworkers (1) in 1957, is an antibiotic active against a variety of the Gram positive and Gram negative bacteria, especially against the mycobacteria, and now widely used as an antituberculous agent. The structure was demonstrated independently by Japanese and American-Canadian groups (2-5) and the absolute configuration was established by Rinehart, Tatsuoka and their associates (6).

Kanamycin-A has the structure of Ia, in which 6-amino-6-deoxy-D-glucose and 3-amino-3-deoxy-D-glucose are linked in the α-form at C-4 and C-6 positions of the 2-deoxy-streptamine moiety respectively.



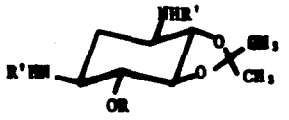
[Ia] R, R', R" = H

[Ib] R = $-CH_2-C_6H_5$, R' = $-\overset{O}{\overset{\|}{C}}-CH_3$, R" = $-\overset{O}{\overset{\|}{C}}-O-CH_2-C_6H_5$

[Ic] R = H , R', R" = $-\overset{O}{\overset{\|}{C}}-CH_3$

Many efforts (7) to synthesize Kanamycin and the related compounds have been attempted in the past ten years. In 1964, we were able to synthesize 2-deoxystreptamine from *cis*-benzene-glycol (5,6-dihydroxy-cyclohexadiene-1,3) (8), and have studied on the synthesis of aminosugar glycosides of cyclitols (9, 10).

In this paper we wish to report the total synthesis of Kanamycin-A and the related compounds.



[IIa] R = H, R' = $-\overset{O}{\overset{\|}{C}}-CH_3$

[IIa'] R, R' = $-\overset{O}{\overset{\|}{C}}-CH_3$

[IIb] R = H, R' = $-\overset{O}{\overset{\|}{C}}-O-CH_2-C_6H_5$

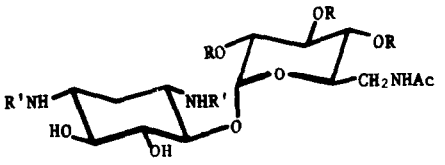
[IIb'] R = $-\overset{O}{\overset{\|}{C}}-CH_3$, R' = $-\overset{O}{\overset{\|}{C}}-O-CH_2-C_6H_5$

Treatment of N,N'-diacetyl- and N,N'-dicarbobenzoxy-2-deoxystreptamine with 2,2-dimethoxy-propane gave the corresponding isopropylidene derivatives (racemic form) in quantitative yield (IIa: m.p. 193-195°, IIb: m.p. 207°) respectively. By acetylation of IIa and IIb were obtained IIa' and IIb', which were converted into diols by hydrolytic removal of the isopropylidene group. Each diol consumed one molar equiv. of periodate, which is compatible with the structure of IIa and IIb. N.m.r. spectrum of IIa showed signals due to the acetamido groups at 7.98τ (3H), 8.02τ (3H) and the isopropylidene group at 8.53τ (6H).

Methyl 3-acetamido-3-deoxy-β-D-glucopyranoside(11) was benzylated with benzylchloride in N,N-dimethylformamide in the presence of potassium hydroxide giving a tribenzyl derivative, which was converted into 3-acetamido-2,4,6-tri-O-benzyl-3-deoxy-D-glucopyranosyl chloride (m.p. 140-143° (dec.), $[\alpha]_D^{25}$ +80° c = 0.5 in $CHCl_3$) by a method similar to that used in the case of the preparation of 6-acetamido-2,3,4-tri-O-benzyl-6-deoxy-D-glucopyranosyl chloride (9).

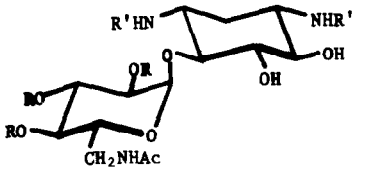
The condensation of IIb with the benzyl derivative of 6-acetamido-6-deoxy-D-glucopyranosyl chloride by a modified Kŏnigs-Knorr reaction and the subsequent removal of the isopropylidene

group produced IIIa (m.p. 220°, $[\alpha]_D^{25}$ +29° c = 2.0 in dioxane, yield 34%) and IVa (m.p. 262°, $[\alpha]_D^{25}$ + 16° c = 2.2 in dioxane, yield 40%). The n.m.r. data of the synthesized glycosides are shown in Table I. Calcd. for $C_{51}H_{57}O_{12}N_3$: C, 67.76; H, 6.36; N, 4.65. Found: IIIa C, 67.97; H, 6.40; N, 5.00. IVa C, 67.72; H, 6.56; N, 4.85.



[IIIa] R = $-CH_2-C_6H_5$, R' = $-\overset{O}{\overset{\|}{C}}-O-CH_2-C_6H_5$

[IIIb] R = H , R' = $-\overset{O}{\overset{\|}{C}}-CH_3$



[IVa] R = $-CH_2-C_6H_5$, R' = $-\overset{O}{\overset{\|}{C}}-O-CH_2-C_6H_5$

[IVb] R = H , R' = $-\overset{O}{\overset{\|}{C}}-CH_3$

The assignment of the α-configuration at C-1' of the glycosides was based on the coupling constant ($J_{1',2'}$) and the chemical shift (12) of the proton at C-1'.

Benzyl and carbobenzoxy groups of IIIa and IVa were hydrolyzed and by subsequent N-acetylation IIIb (m.p. >200°) and IVb (m.p. >220°) were obtained respectively. Their n.m.r. data are shown in Table I. The condensation of IIIa with 3-acetamido-2,4,6-tri-O-benzyl-3-deoxy-D-glucopyranosyl chloride by a modified Königs-Knorr reaction gave Ib (m.p. 222-223°, $[\alpha]_D^{25}$ + 50° c = 0.5 in pyridine, yield 25%) and Va (m.p. 255°, yield 20%). Calcd. for $C_{80}H_{88}O_{17}N_4$: C, 69.75; H, 6.44; N, 4.07. Found for Ib: C, 69.55; H, 6.61; N, 4.19.

Table I. The N.M.R. Data (τ)
of Anomeric and Acetamido Protons of the Synthesized Glycosides

Compound	Solvent	Anomeric Protons	Acetamido Protons
Ic	D_2O	4.65 [3.0][a], 4.86 [4.0]	7.96 (6)[b], 8.00 (3), 8.05 (3)
IIIa	d-6-DMSO	4.25 [3.5]	8.10 (3)
IIIb	D_2O	4.80 [2.0]	8.00 (6), 8.08 (3)
IVa	d-6-DMSO	4.58 [3.0]	8.15 (3)
IVb	D_2O	4.93 [3.5]	7.97 (3), 8.00 (3), 8.02 (3)
Vb	D_2O	4.65 [2.5], 4.88 [1.5]	7.97 (6), 8.01 (6)

[a]Number in parentheses [ ] is the J_{12} coupling constant of doublet in cps.

[b]Number in parentheses ( ) is refer to number of protons.

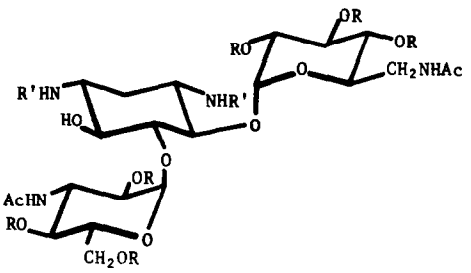
Removal of the benzyl and carbobenzoxy groups of Ib with sodium in liq. ammonia at -70° and the subsequent N-acetylation gave compound (Ic) (m.p. >240°, $[\alpha]_D^{25}$ + 115° c = 0.52 in H_2O). The n.m.r. data is shown in Table I. Infrared and n.m.r. spectra, specific rotatory power $[\alpha]_D$, Rf values of the thin-layer chromatograms and o.r.d. curve of Ic are all identical with those of the authentic sample of tetra-N-acetyl-Kanamycin-A.

Hydrolysis of Ic with barium hydroxide gave Ia (amorphous), which showed the same Rf value on thin-layer chromatograms as that of the authentic sample of free base of Kanamycin-A and was active against *Bacillus subtilis* (IFO 3007) and *Escherichia coli* (IFO 3208).

By the same treatment of Va as mentioned above was obtained Vb (m.p. >200°, $[\alpha]_D^{25}$ + 55° c = 0.6 in H_2O) which carries signals corresponding to the anomeric protons of the α-glucosides at 4.65τ (d, J = 2.5 cps), 4.88τ (d, J = 1.5 cps) as shown in Table I. The results have suggested that, in Vb, 3-acetamido-3-deoxy-D-glucose is linked in the α-form at C-5 of the 2-deoxystreptamine moiety of IIIb.

It should be noted that no β-glycoside was isolated in the above mentioned glycosidation by a modified Königs-Knorr reaction. The details will be published in *Agr. Biol. Chem. (Tokyo)*.

We wish to thank Professor Tetsuo Mitsui, Department of Food Science and Technology for elemental analyses and Dr. Tetsuro Shingu, College of Pharmacy for n.m.r. measurements.



[Va] R = $-CH_2-C_6H_5$, R' = $-\overset{O}{\overset{\|}{C}}-O-CH_2-C_6H_5$

[Vb] R = H , R' = $-\overset{O}{\overset{\|}{C}}-CH_3$

References

1. H.Umezawa, M.Ueda, K.Maeda, K.Yagishita, S.Kondo, Y.Okami, R.Utahara, Y.Osato, K.Nitta, and T.Takeuchi, *J.Antibiotics*, 10A, 181 (1957).
2. M.J.Cron, D.L.Evans, F.M.Palermiti, D.F.Whitehead, I.R.Hooper, P.Chu, and R.U.Remieux, *J.Am.Chem.Soc.*, 80, 4741 (1958).
3. K.Maeda, M.Murase, H.Mawatari, and H.Umezawa, *J.Antibiotics*, 11A, 163 (1958).
4. H.Ogawa, T.Ito, S.Kondo, and S.Inoue, *J.Antibiotics*, 11A, 169 (1958).
5. S.Umezawa, Y.Ito, and S.Fukatsu, *J.Antibiotics*, 11A, 162 (1958).
6. M.Hichens and K.L.Rinehart,Jr., *J.Am.Chem.Soc.*, 85, 1547 (1963).
   S.Tatsuoka, S.Horii, K.L.Rinehart,Jr., and T.Nakabayashi, *J.Antibiotics*, 17A, 88 (1964).
7. S.Umezawa and S.Koto, *Bull.Chem.Soc.Japan*, 39, 2014 (1966)
   S.Umezawa, K.Tatsuta, T.Tsuchiya, and E.Kitazawa, *J.Antibiotics*, 20A, 53 (1967).
   T.Suami, S.Ogawa, and H.Sano, *Tetrahedron Letters*, 2671 (1967).
8. M.Nakajima, A.Hasegawa, and N.Kurihara, *Tetrahedron Letters*, 967 (1964).
   Ann., 689, 235 (1965).
9. T.Ueno, N.Kurihara, S.Hashimoto, and M.Nakajima, *Agr.Biol.Chem.(Tokyo)*, in press.
10. H.Shibata, N.Kurihara, and M.Nakajima, in preparation.
11. H.H.Baer, *J.Am.Chem.Soc.*, 83, 1882 (1961).
12. J.M.van der Veen, *J.Org.Chem.*, 28, 564 (1963).