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SYNTHESIS OF KASUGANOBIOSAMINE

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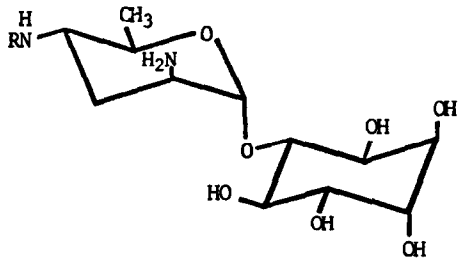
Kasugamycin, discovered by Umezawa and his coworkers (1) in 1965, is an aminoglycoside antibiotic exhibiting a selective inhibitory effect against *Piricularia oryzae*, and now widely used as an anti-rice blast agent in Japan.

The structure (2) was elucidated by means of degradation studies as well as physical methods such as X-ray analysis, and the absolute configuration (Ia) was established so that the aminosugar moiety was linked by an α-glycosidic linkage to (+)-inositol at its C-5 posision* It was also demonstrated (2f) that hydrolysis of Ia by barium hydroxide gave kasuganobiosamine (Ib) which gave the dihydrochloride of Ia reversibly by treating with oxaldiimidic acid diethyl esterand subsequent mild hydrolysis with hydrochloric acid. In this paper, we wish to report the synthesis of kasuganobiosamine (Ib) which means the total synthesis of kasugamycin (Ia) together with the introduction of the oxalimidyl group into Ib described above.



Ia R = -C(=NH)-COOH

b R = H

* The numbering of (+)-inositol is due to the method proposed by H.G.Fletcher, Jr., L.Anderson, and H.A.Lardy, *J.Org.Chem.*, 16, 1238 (1951)

Methyl 4,6-O-benzylidene-2-O-*p*-tolylsulfonyl-3-deoxy-α-D-glucopyranoside (IIa) (3) derived via five steps from D-glucose, was refluxed in N,N-dimethyl formamide (DMF) with sodium azide to give an azide (IIb) (ν_{N_3} = 2170 cm^{-1}, film) accompanying the Walden inversion. The azide was hydrogenated over platinum catalyst in methanol followed by acetylation to give the corresponding acetamido derivative (IIc) (m.p. 174-175°, $[\alpha]_D^{16}$ + 73.1° c = 1.0 in $CHCl_3$). The configuration of IIc was assigned by means of n.m.r. spectrum in $CDCl_3$. The anomeric proton signal at 5.48τ* showed a splitting value of 0.8 cps (doublet) which is characteristic to that observed between equatorial C-1 and C-2 protons of methyl 4,6-O-benzylidene-α-D-hexopyranosides (4).

Methyl 2-acetamido-2,3-dideoxy-α-D-mannopyranoside (IIIa) was obtained as an oil by hydrolytic removal of the benzylidene group of IIc in warm aqueous sulfuric acid. IIIa was treated with *p*-toluenesulfonyl chloride (1.2 mole) in dry pyridine followed by acetylation to afford IIIb (m.p. 140-141°, $[\alpha]_D^{32}$ + 71.3° c = 1.0 in $CHCl_3$) in 55% yield. IIIb was heated with sodium iodide and acetone in a sealed tube at 100°C to give the corresponding iodide. The catalytic hydrogenation of the iodide with the Raney Ni W-2 in the presence of Amberlite IR-45(OH^- form) in methanol gave an oily product which was then deacetylated with sodium methoxide in methanol to IIIc as a syrup. The oxidation of IIIc with chromic acid gave an oxo-compound, which was hydrogenated over platinum catalyst and converted to methyl 2-acetamido-2,3,6-trideoxy-α-D-talopyranoside (IVa) (m.p. 121-122.5°) in 65% yield where the configuration of the newly formed hydroxyl group at C-4 was axial. The mesylate (IVb) which was obtained by the treatment of IVa with methanesulfonyl chloride in pyridine was refluxed with sodium azide in DMF affording an oily azide (ν_{N_3} = 2140 cm^{-1}, film). Hydrogenation of the azide over platinum catalyst in methanol followed by acetylation gave methyl 2,4-diacetamido-2,3,4,6-tetradeoxy-α-D-mannopyranoside (V) (m.p. 194.5-196°, $[\alpha]_D^{24}$ + 100° c = 1.0 in H_2O). Calcd. for $C_{11}H_{20}O_4N_2$: C, 54.08; H, 8.25; N, 11.47. Found : C, 54.22; H, 8.39; N, 11.57. The n.m.r. spectrum of V in D_2O showed two acetamido signals at 7.97τ and 8.02τ assigned to C-2 axial and C-4 equatorial acetamido groups respectively and an anomeric proton signal at 5.40τ (doublet, $J_{1,2}$ = 1.2 cps) which supported a methyl α-D-mannopyranoside structure. Methyl N,N'-diacetyl-α-kasugaminide (m.p. 195.5-196.5°, $[\alpha]_D^{24}$ + 98° c = 1.0 in H_2O) prepared by the methanolysis of heptaacetyl kasuganobiosamine and

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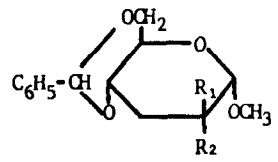
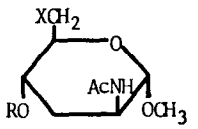
* Chemical shifts herein reported are relative to tetra-methylsilane (in $CDCl_3$) or sodium 2,2-dimethyl silapentane sulfonate (in D_2O) as an internal standard.

subsequent acetylation was identical with V in the infrared and n.m.r. spectra, and showed no depression of mixed melting point.

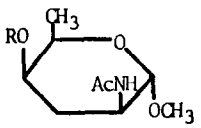
N,N'-Diacetyl kasugamine obtained by the hydrolysis of V with 5N-formic acid was acetylated to the triacetate (VIa) which was dissolved in a mixture of chloroform and acetic acid saturated with hydrogen chloride and warmed at 30-40° for 5 hours to give the chloride (VIb). VIb and 1:2,3:4-di-O-isopropyridene-(+)-inositol prepared by the method of Angyal (5) were stirred at 30° for 50 hours in chloroform in the presence of Ag_2CO_3, $AgClO_4$ and Drierite to give a glycoside (VII) (m.p. 155-160°, $[\alpha]_D^{12}$ + 91.6° c = 1 in ethanol). The n.m.r. spectrum of VII in $CDCl_3$ indicates the presence of 3 protons of C-6 (8.84τ, doublet $J_{5,6}$ = 5.0 cps), two isopropylidene groups (8.64τ, 8.50τ), two acetamido groups (8.00τ, somewhat broad) and C-1 proton (5.00τ, doublet $J_{1,2}$ = 1.4 cps). The hydrolytic removal of the isopropylidene groups of VII with 50% aqueous acetic acid followed by acetylation gave a heptaacetyl compound (m.p. 150-152°, $[\alpha]_D^{15}$ + 34.5° c = 1.0 in ethanol). Calcd. for $C_{26}H_{31}O_{14}N_2$: C, 51.58; H, 6.44. Found: C, 51.85; H, 6.56. This compound was identical with the authentic sample of heptaacetyl kasuganobiosamine prepared from kasugamycin in the infrared and n.m.r. spectra, specific rotatory power and melting point. Methanolysis of the heptaacetate with sodium methoxide in methanol gave N,N'-diacetyl kasuganobiosamine which was then deacetylated by refluxing in aqueous barium hydroxide for ten hours to give kasuganobiosamine, crystallized as the dihydrochloride (m.p. 225-230° (dec.), $[\alpha]_D^{15}$ + 103° c = 1.8 in H_2O ; lit.(2c) m.p. 222-225° (dec.), $[\alpha]_D^{15}$ + 101° c = 1.8 in H_2O).



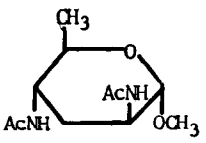
IIa R_1 = H; R_2 = OTs
b R_1 = N_3; R_2 = H
c R_1 = NHAc; R_2 = H



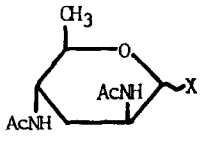
IIIa R = H; X = OH
b R = Ac; X = OTs
c R = X = H



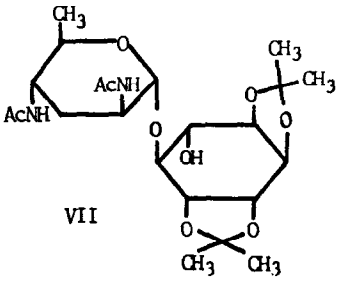
IVa R = H
b R = Ms



V



VIa X = OAc
b X = Cl



VII

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