Tetrahedron Letters No.45, pp. 3969-3972, 1969. Pergamon Press. Printed in Great Britain.

A SYNTHESIS OF d-DIACETYLMETHYLKASUGAMINIDE[1)]

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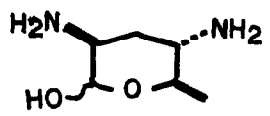
(Received in Japan 11 August 1969; received in UK for publication 25 August 1969)

Optically active and racemic derivatives of kasugamine 1, the diamino-sugar moiety of kasugamycin,[2)] have been prepared from glucose[3)] and from 6-methyl-3,4-dihydro-2H-pyran-2-one[4)] respectively. In this paper we should like to report a synthesis of d-diacetylmethylkasugaminide.[3)]

2-Ethoxy-6-methyl-3,4-dihydro-2H-pyran 2,[5)] obtainable from methyl vinyl ketone and ethyl vinyl ether, was at first hydroborated in THF to give an adduct 3. Subsequent treatment of the adduct with chloramine in ether afforded an amine 4 and an alkylboric acid 5. the former amine was isolated as the acetyl compound 6[6)] (12 % from 2), m.p. 160 - 161° (ν_{max}^{nujol} 3270, 1640, 1565 cm^{-1}, τ^{CDCl_3} 3.98 (3H, s), 5.5 (1H, q, J = 9 +3Hz), 4.25 (1H, br s)) while the boric acid 5 was oxidized with H_2O_2 in alkaline solution to produce an alcohol 7 (55 % from 2). The alcohol 7 was converted to the acetamide 8 m.p. 104 - 105° (ν_{max}^{nujol} 3220, 1640 1560 cm^{-1}, τ^{CDCl_3} 8.0 (3H, s), 5.24 (1H, t, J =2Hz), 4.54 (1H, br s)) by the sequence of reactions involving oxidation (CrO_3-pyridine) to ketone, (55.6 %, semicarbazone, m.p. 173.5 -175°), formation of oxime, reduction (Na - EtOH) and subsequent acetylation (48.5 % from the ketone).

On treatment with bromine in ethanol containing hydrogen chloride at 65 -70° for 3 days, the acetamide 6 (or 8) gave three bromo compounds, 9, m.p. 152.5 - 154° (ν_{max}^{nujol} 3240, 1645, 1545 cm^{-1}, τ^{CDCl_3} 8.02 (3H, s), 5.6 (1H, d, J = 9Hz), 3.9 (1H, br s)), 10, m.p. 139 - 139.5° (ν_{max}^{nujol} 3180, 1645, 1540 cm^{-1}, τ^{CDCl_3} 8.02 (3H, s), 5.27 (1H, d, J = 3Hz), 4.3 (1H, br s)) and 11, m.p. 138 - 139° (ν_{max}^{nujol} 3240, 1640, 1550 cm^{-1}, τ^{CDCl_3}



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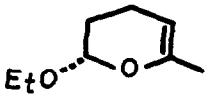

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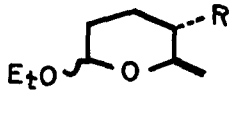
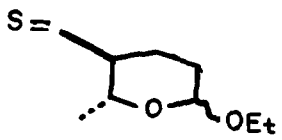
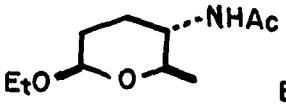


3 R = BS_2

4 R = NH_2

5 R = B_S^{OH}





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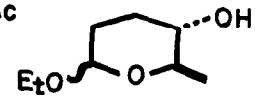

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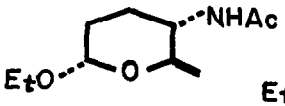

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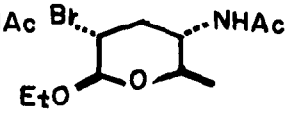

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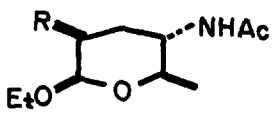
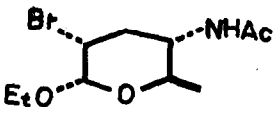


12 R = N_3

13 R = NH_2

14 R = NHAc



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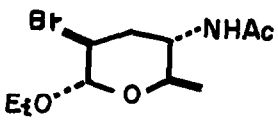

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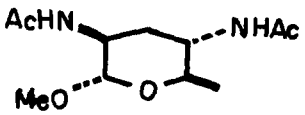

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Figure

7.95 (3H, s), 5.15 (1H, d, J = 1.5Hz), 3.8 (1H, br s)) in 21, 17 and 30 % yield, respectively. The doublet at τ 5.60 with J = 9Hz in the nmr spectrum of 9 indicates the diequantorial disposition of Br and OEt. Treatment of either 9 or 10 with saturated ethanolic solution of hydrogen chloride afforded an equilibrated mixture of 9 and 10 in a ratio of about 4:3. Therefore, the configuration of 10 is expressed as shown in the Figure. The diaxial configuration of Br and OEt in 11 is suggested by the coupling constant J = 1.5Hz, and as expected, treatment of 11 with NaBr in HMPA at 95 - 100° for several days gave an equilibrium mixture of 10 and 11, in a ratio of 2:3. Thus both the isomers 10 and 11 are converted to 9.

Reaction of 9 with NaN_3 in DMSO at 100 - 105° for 3 days yielded an azide 12 (67 %), m.p. 180 - 180.5° (ν_{max}^{nujol} 3300, 2140, 2110, 1640, 1555 cm^{-1}, τ^{CDCl_3} 8.03 (3H, s), 5.4 (1H, d, J = 1.7Hz)). Catalytic hydrogenation (PtO_2) of 12 in ethanol produced an amine 13, which afforded diacetyl derivative 14, m.p. 171 - 172.5° (ν^{neat} 3220, 1640, 1545 cm^{-1}, τ^{CDCl_3} 8.02 (3H, s), 7.98 (3H, s), 5.45 (1H, d, J = 2.5Hz)) in 72 % yield from 12. The compound 14 was completely identical with the optical active form, m.p. 227.5 - 229°, derived from kasugamycin in thin layer chromatography, ir and nmr spectra.

Optical resolution of amine 13 was effected with D-(-)-tartaric acid. The sparingly soluble salt was decomposed by 2N-NaOH solution at 50°. Acetylation of the resolved amine gave the optical active diacetyl derivative 14, in 44 % yield from 13. The optical active 14 was converted into α-methyl glycoside 15, m.p. 193.5 - 195° ($[\alpha]_D^{22}$ +107° (c = 1.0, MeOH)) in methanol saturated with hydrogen chloride in 60 % yield. The synthesis of d-15 means the total synthesis of kasugamycin, since d-15 had been already condensed with a d-inositol derivative to give kasuganobiosamine[3),7)] which in turn had been converted to kasugamycin.[2c)] Since the intermediate 6 can be readily obtained by hydroboration-amination as described above, the synthesis provides a simple route to synthetic kasugamycin.

REFERENCES AND NOTES

1) Presented before the 22th annual meeting of the Chemical Society of Japan, on Apr. 4, 1969.

2) (a) Y. Suhara, K. Maeda and H. Umezawa, J. Antibiotics, 18A, 182 (1965).
(b) Y. Suhara, K. Maeda, H. Umezawa and M. Ohno, ibid., 18A, 184 (1965).
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5) R. I. Longley, Jr. and W. S. Emerson, J. Am. Chem Soc., 72, 3079 (1950).

6) All the crystalline new compounds in this paper gave satisfactory elemental analysis and spectroscopic data.

7) Y. Suhara et al, also reported a synthesis of kasuganobiosamine through a different intermediate.[4)]