Synthesis of a Derivative of Vancosamine, a Component of the Glycopeptide Antibiotic Vancomycin

By TON THAT THANG* and FRANCOIS WINTERNITZ
(*Equipe de recherche No.* 195, *C.N.R.S., 8 rue Ecole Normale, Montpellier Cedex* 34075, *France*)
and ALAIN OLESKER, ALAIN LAGRANGE, and GABOR LUKACS
(*Institut de Chimie des Substances Naturelles du C.N.R.S.*, 91190-*Gif-sur-Yvette, France*)

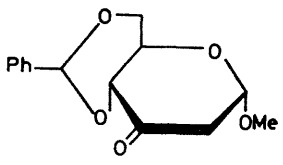
Summary A derivative of the branched-chain sugar 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose (vancosamine) has been synthesised.

CONSIDERABLE effort has been recently directed[1,2] towards the synthesis of the unusual branched-chain sugar 3-amino-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexose (vancosamine)[3] (**17**), a component of the antibiotic vancomycin.[4] We report here the first stereospecific synthesis of a derivative (**16**) of vancosamine (**17**).

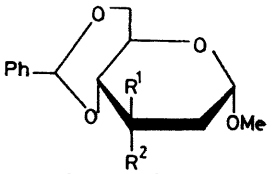
The addition of KCN to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**1**), under conditions of thermodynamic control in CH_2Cl_2 solution in the presence of $NaHCO_3$ and water, followed by mesylation furnished a product (**3**) belonging to the *arabino*-series as shown by ^{13}C n.m.r. spectroscopy, yield 76% (m.p. 169—171 °C, $[\alpha]_D$ + 95°). In contrast, the addition of HCN to (**1**), under kinetic control, in pyridine solution, followed by mesylation has been shown by Yoshimura *et al.*[5] to afford a compound (**2**) with the *ribo*-configuration. This reaction was repeated, using the method of Bourgeois,[2] and (**2**) and (**3**) were transformed with configurational inversion[1b] through the corresponding spiro-aziridines (**4**)[5] and (**5**) into the amines (**6**)[5] (oil, $[\alpha]_D$ + 89°) and (**7**) (m.p. 97—99 °C, $[\alpha]_D$ + 75°), respectively, with overall yields of 67%.

The stereochemistry at C-3 of (**6**) has been unambiguously established from chemical evidence.[5] ^{13}C N.m.r. spectroscopy may be used to determine the configuration of substituents on quaternary centres[6] and this technique was used to establish the structure of (**7**) and to confirm that of (**6**).[5] Carbon signal assignments for (**6**) and (**7**) and for the models (**8**)[7] and (**9**)[7] are in the Table.† The characteristic chemical shift differences observed between the corresponding carbon signals of the two models (**8**) and (**9**) (especially C-4, C-5, and 3-Me) are also exhibited by the spectra of the amines (**6**) and (**7**). The axial *C*-methyl carbons resonate at higher field than their equatorial counterparts and a greater steric compression effect is experienced by C-5 when its hydrogen interacts 1,3-diaxially with a C(3)–heteroatom linkage as in (**7**) and in (**9**) than with a C(3)–carbon bond as in (**6**) and in (**8**).[8]

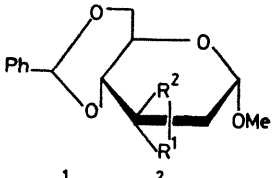
The amine (**7**) was readily acetylated to (**10**) (oil, $[\alpha]_D$ +104°) which, with *N*-bromosuccinimide, gave methyl 3-acetamido-4-*O*-benzoyl 6-bromo-2,3,6-trideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside (**11**) in 89% yield (m.p. 141 °C, $[\alpha]_D$ + 22°). Catalytic hydrogenation of (**11**) gave (**12**) (oil, $[\alpha]_D$ + 55°) which, upon alkaline hydrolysis, furnished (**13**) (m.p. 134—135 °C, $[\alpha]_D$ + 41°) in 85% yield from (**11**).



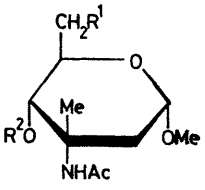
(1)



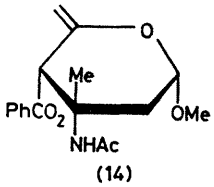
(2) R^1 = CN, R^2 = $MeSO_3$
(3) R^1 = $MeSO_3$, R^2 = CN
(6) R^1 = NH_2, R^2 = Me
(7) R^1 = Me, R^2 = NH_2
(8) R^1 = OH, R^2 = Me
(9) R^1 = Me, R^2 = OH
(10) R^1 = Me, R^2 = NHAc



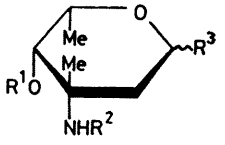
(4) R^1 = CH_2, R^2 = NH
(5) R^1 = NH, R^2 = CH_2



(11) R^1 = Br, R^2 = PhCO
(12) R^1 = H, R^2 = PhCO
(13) R^1 = H, R^2 = H



(14)



(15) R^1 = PhCO, R^2 = Ac, R^3 = β-OMe
(16) R^1 = H, R^2 = Ac, R^3 = β-OMe
(17) R^1 = H, R^2 = H, R^3 = OH

TABLE. ^{13}C Chemical shifts.[a]

Carbon	(6)	(7)	(8)	(9)	(13)	(16)
C-1	98·9	99·0	99·0	99·0	97·9	100·2
C-2	43·4	41·6	42·6	41·8	42·4	37·3
C-3	49·9	49·2	69·5	68·5	57·0	55·9
C-4	86·6	84·1	85·5	83·3	79·9	72·6
C-5	61·2	59·4	61·8	59·7	66·5	68·9
C-6	69·5	69·3	69·5	69·4	17·5	17·1
3-Me	22·9	28·0	22·8	25·3	24·0	21·6
OMe	55·0	55·1	55·1	55·4	55·0	56·5
NH–*C*OMe	—	—	—	—	172·7	170·4
NH–COMe	—	—	—	—	23·3	24·3

[a] Benzylidene carbon signals appear for (**6**), (**7**), (**8**), and (**9**) at 101·9 ± 0·3, 2 × 126·3 ± 0·2, 2 × 128·3 ± 0·2, 129·1 ± 0·2, and 137·7 ± 0·2.

† ^{13}C N.m.r. spectra were recorded in $CDCl_3$ solution on a Bruker HX-90 Fourier transform spectrometer. Chemical shifts are given in p.p.m. with respect to Me_4Si as internal standard. $[\alpha]_D$ values were measured in $CDCl_3$ solution at room temperature.

Dehydrobromination of (**11**) as described by Horton and Weckerle[9] gave the 5,6-unsaturated glycoside (**14**) (m.p. 136—138 °C, $[\alpha]_D$ + 117°) in 95% yield. The ethylenic double bond of this compound was hydrogenated in the presence of Raney nickel yielding 78% of (**15**) (m.p. 83—85 °C, $[\alpha]_D$ − 13°) and 7·8% of (**12**) which could be separated by chromatography. Hydrolysis of the benzoate group of (**15**) furnished the desired product, methyl 3-acetamido-2,3,6-trideoxy-3-*C*-methyl-β-L-*lyxo*-hexopyranoside (**16**) (m.p. 133—134 °C, $[\alpha]_D$ + 46°).

The ^{1}H n.m.r. spectra of (**13**) and (**16**) are in excellent agreement with the structures assigned. In the ^{13}C n.m.r. spectrum of (**16**) the C-1, C-5, and OMe signals are deshielded while the C-2, C-4, and 3-Me signals are characteristically shielded with respect to the corresponding carbon resonances of (**13**)[10] (Table). These differences reflect unambiguously the equatorial configuration of the anomeric substituent and the axial configuration of the C-4 and 3-Me substituents of (**16**).

(*Received, 11th September* 1978; *Com.* 986.)

[1] (a) J. S. Brimacombe and L. W. Doner, *J.C.S. Perkin I*, 1974, 62; J. S. Brimacombe, J. A. Miller, and U. Zakir, *Carbohydrate Res.*, 1975, **41**, C3; 1975, **44**, C9; (b) *ibid.*, 1976, **49**, 233.
[2] J. M. Bourgeois, *Helv. Chim. Acta*, 1973, **56**, 2879; 1974, **57**, 2553; 1975, **58**, 363; 1976, **59**, 2114.
[3] R. M. Smith, A. W. Johnson, and R. D. Guthrie, *J.C.S. Chem. Comm.*, 1972, 361; A. W. Johnson, R. M. Smith, and R. D. Guthrie, *J.C.S. Perkin I*, 1972, 2153; W. D. Weringa, D. H. Williams, J. Feeney, J. P. Brown, and R. W. King, *ibid.*, p. 443.
[4] D. H. Williams and J. R. Kalman, *J. Amer. Chem. Soc.*, 1977, **99**, 2768 and references cited therein.
[5] J. Yoshimura, M. Matsuzawa, K. Sato, and M. Funabashi, *Chem. Letters*, 1977, 1403.
[6] A. M. Sepulchre, B. Septe, G. Lukacs, S. D. Gero, W. Voelter, and E. Breitmaier, *Tetrahedron*, 1974, **30**, 905.
[7] B. Flaherty, W. G. Overend and N. R. Williams, *Chem. Comm.*, 1966, **43**; *J. Chem. Soc.* (*C*), 1966, 398.
[8] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972.
[9] D. Horton and W. Weckerle, *Carbohydrate Res.*, 1975, **44**, 227.
[10] S. Omura, A. Nakagawa, A. Neszmelyi, S. D. Gero, A. M. Sepulchre, F. Piriou, and G. Lukacs, *J. Amer. Chem. Soc.*, 1975, **97**, 4001; S. Omura, A. Neszmelyi, M. Sangaré, and G. Lukacs, *Tetrahedron Letters*, 1975, 2939.