

1-Acetyl-*t*-3,*t*-4-isopropylidenedioxy-*c*-4-hydroxymethyl-*r*-2-methoxypyrrolidine: a Branched-chain Sugar with Nitrogen as the Ring Hetero-atom†

By M. H. HALFORD,* D. H. BALL, and L. LONG, JUN.

(Pioneering Research Laboratory, U.S. Army Natick Laboratories, Natick, Massachusetts 01760)

RECENTLY, we described¹ the preparation of methyl 2,3-*O*-isopropylidene-4-thio- β -D-apio-D-furanoside, the first example of a branched-chain sugar with an atom other than oxygen in the hemiacetal ring. We have now synthesised the title compound, an analogous apiose derivative with nitrogen as the ring hetero-atom.

Treatment of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulphonyl- α -D-apio-L-furanose² (I) with sodium azide in aqueous acetone afforded 5-azido-5-deoxy-1,2-*O*-isopropylidene- α -D-apio-L-furanose (II), m.p. 50—50.5°; $[\alpha]_D^{24} + 76^\circ$ (*c* 1.0, EtOH); $\nu_{\max}(\text{KBr})$ 2100 cm^{-1} (N_3).‡ Reduction of azide

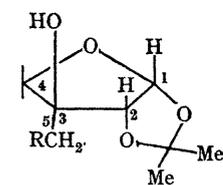
(II), with an excess of Raney nickel in methanol,³ followed by *N*-acetylation yielded 5-acetamido-5-deoxy-1,2-*O*-isopropylidene- α -D-apio-L-furanose (III), m.p. 75—77°; $[\alpha]_D^{24} + 81^\circ$ (*c* 1.0, EtOH); $\nu_{\max}(\text{KBr})$ 3300 (OH, NH), 1640, and 1570 cm^{-1} (NHAc).

Treatment of (III) with 2% methanolic HCl at 25° resulted in a mixture of three components which were separated by silica gel column chromatography. The major product, methyl 5-acetamido-5-deoxy- β -D-apio-L-furanoside (IV), m.p. 135—136°; $[\alpha]_D^{26} - 121^\circ$ (*c* 1.0, MeOH); $\nu_{\max}(\text{KBr})$ 1630 and 1580 cm^{-1} (NHAc), was obtained (40%) from

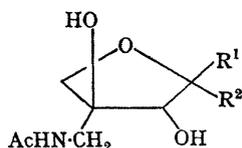
† Part of a series on the chemistry of apiose; for previous Part, see ref. 1.

‡ All compounds reported gave satisfactory elemental analyses.

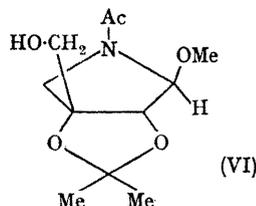
(III). Also formed [15% yield from (III)] was the corresponding α -glycoside (V), m.p. 164–165°; $[\alpha]_D^{26} + 130^\circ$ (*c* 0.6, MeOH); ν_{\max} (KBr) 1630 and 1550 cm^{-1} (NHAc).



- (I) $\text{R}=\text{O}\cdot\text{SO}_2\cdot\text{C}_6\text{H}_4\text{Me}-p$
 (II) $\text{R}=\text{N}_3$
 (III) $\text{R}=\text{NHAc}$



- (IV) $\text{R}^1=\text{OMe}, \text{R}^2=\text{H}$
 (V) $\text{R}^1=\text{H}, \text{R}^2=\text{OMe}$



(VI)

The third, fastest-moving component, isolated as a mobile syrup, crystallized after distillation (105°/0.1 mm.). Recrystallization from carbon tetrachloride yielded 1-acetyl-*t*-3,*t*-4-isopropylidenedioxy-*c*-4-hydroxymethyl-*r*-2-methoxy-pyrrolidine§ (VI), m.p. 61–63°; $[\alpha]_D^{25} + 9^\circ$ (*c* 1.0, CHCl_3) [25% yield from (III)]. The i.r. spectrum (KBr) showed absorption at 3400 (OH), a doublet at 1370, 1382 cm^{-1} (CMe_2) and an amide I band at 1620 cm^{-1} . No amide II band was observed.

The n.m.r. spectrum¶ of (VI), measured in deuteriochloroform at the ambient probe temperature, was unusually complex and clearly indicated the presence of two isomers in solution; it showed τ 8.59 (s, CMe_2), 7.84 (s) and 7.91 (s) (NAc), 6.65 (s) and 6.63 (s) (OMe), 5.02 (s) and 4.46 (s) (anomeric H), 5.74 (s) and 5.60 (s) (H-3), and 7.79 br (s, OH). The addition of trichloroacetyl isocyanate caused the disappearance of the hydroxy-proton signal and the appearance of a singlet (1H) at τ 1.49 (NH). The signals of the CH_2O group, initially two broad singlets at τ 6.27 and 6.25, were shifted downfield and appeared as two AB quartets centered at τ 5.56 and 5.51 (*J* 12 and 11 Hz, respectively).

The n.m.r. spectrum of (VI) measured in bistrideuterio-methyl sulphoxide at the ambient probe temperature was

§ *t* means *trans*, *c* means *cis*, and *r* means reference atom.

¶ Measured at 100 MHz and with internal Me_4Si .

¹ M. H. Halford, D. H. Ball, and L. Long, jun., *Carbohydrate Res.*, 1968, **8**, 363.

² D. H. Ball, F. A. Carey, I. L. Klundt, and L. Long, jun., *Carbohydrate Res.*, in the press.

³ M. L. Wolfrom, J. Bernsmann, and D. Horton, *J. Org. Chem.*, 1962, **27**, 4505.

⁴ W. A. Szarek, S. Wolfe, and J. K. N. Jones, *Tetrahedron Letters*, 1964, 2743.

⁵ H. Paulsen and K. Todt, *Chem. Ber.*, 1967, **100**, 3385, 3397.

⁶ S. Hanessian, *J. Org. Chem.*, 1967, **32**, 163.

similar to that in deuteriochloroform, except that two peaks at τ 8.32 and 8.28 were observed for the CMe_2 protons and the hydroxy-protons gave two closely-spaced triplets at τ 4.67 and 4.65. The two H-2 resonances appeared at τ 4.53 and 4.32 and those of H-3 at τ 5.35 and 5.24. The methoxy-protons (τ 6.39 and 6.33) and the acetyl protons (τ 7.60 and 7.53) again exhibited doublet patterns. The spectrum, measured with the high-field band of the CMe_2 signal (τ 8.32) as reference for the internal lock (Me_4Si omitted), is shown in the Figure. The appearance of the 2-, 3-, and hydroxy-proton resonances at temperatures above ambient probe

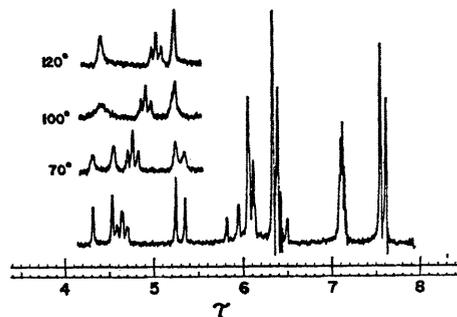


FIGURE. Partial 100 MHz n.m.r. spectrum of the title compound (VI) in bistrideuteriomethyl sulphoxide.

temperature is also shown. When the temperature of the sample was raised, the OH resonances collapsed to a single triplet which moved upfield. At 70°, the two H-2 and the two H-3 resonances had not coalesced, and the methoxy- and acetyl signals still exhibited doublet patterns. At 100°, the methoxy- and acetyl proton resonances had collapsed to singlets at τ 6.33 and 7.56 respectively, and H-2 gave a broad singlet at τ 4.43 and H-3 a singlet at τ 5.25. The H-2 and H-3 resonances were sharpened by a further rise in temperature. The original pattern was restored by cooling.

The above experiments demonstrate the presence of two isomers of (VI) in solution at temperatures below *ca.* 70°. Such isomerism, due to restricted rotation about the C–N bond, has been observed previously for several carbohydrates containing nitrogen as the ring heteroatom.^{4–6}

We thank the National Academy of Sciences, National Research Council for a Research Associateship (to M. H. H.) and Mr. F. H. Bissett and Dr. R. C. Chalk for assistance with the n.m.r. spectra.

(Received, January 6th, 1969; Com. 012.)