Synthesis of Cyano-sugars: A Route to Branched-chain Sugars

By B. E. DAVIDSON, R. D. GUTHRIE,* and A. T. MCPHAIL
(*School of Molecular Sciences, University of Sussex, Brighton* BN1 9QJ)

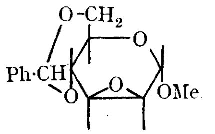
As a potential route for the introduction of a variety of branched chains into monosaccharides, we are investigating methods of preparing cyano-sugars. During these studies, Williams published a Communication on this topic.[1]

Opening of the epoxide ring in methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannoside (I) and the corresponding alloside was first attempted with potassium cyanide in *NN*-dimethylformamide. Extensive decomposition occurred over a wide range of temperatures, and no recognizable products could be isolated.

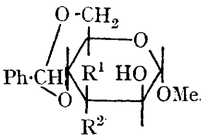
Attention was then turned to the use of aluminium triethyl and hydrogen cyanide in tetrahydrofuran, a reagent system used with great success for the opening of many steroid epoxides.[2] Use of this reagent on epoxide (I) gave a mixture of two products, separable by chromatography on silica gel. One component (52%) was shown to be methyl 4,6-*O*-benzylidene-3-cyano-3-deoxy-α-D-altroside (II),† m.p. 150—150·5°, $[\alpha]_D + 159°$, the product from the expected[3] diaxial ring-opening of such an epoxide. The *altro*-configuration was established from its n.m.r. spectrum and from a three-dimensional *X*-ray structural study on the 2-*O*-bromoplenylsulphonyl derivative, $C_{21}H_{20}BrNO_7S$. The crystals are triclinic, space group $P1$, $a = 6{\cdot}05$, $b = 7{\cdot}39$, $c = 12{\cdot}62$ Å, $\alpha = 105{\cdot}6$, $\beta = 97{\cdot}4$, $\gamma = 92{\cdot}3°$. The structure was solved by the heavy-atom method employing intensity data visually estimated from equi-inclination Weissenberg photographs taken with Cu-K_α radiation. Several cycles of block-diagonal least-squares refinement of the co-ordinates and thermal parameters (anisotropic for the bromine atom, isotropic for the remainder) resulted in an *R* value of 12·3% over 1810 independent structure amplitudes. The co-ordinates yield satisfactory bond lengths and valency angles.

The second syrupy product (11%) from ring-opening of (I) was shown from an n.m.r. and mass spectral study on it (M^+ 434·905; $C_{23}H_{33}NO_7$ requires 434·905) and its acetate (M^+ 477·234; $C_{25}H_{35}NO_8$ requires 477·236) to have the partial structure (IV) in which a dimer of tetrahydrofuran has been incorporated into the molecule. Varying the reaction time did not greatly affect the proportions of (II) and (IV) formed. However, when ether was used as solvent, only compound (II) was formed (65% after recrystallisation).

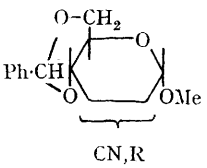
Extension of the use of the aluminium triethyl–hydrogen cyanide in ether system to the ring-opening of methyl 2,3-anhydro-β-L-ribopyranoside (V) gave methyl 3-cyano-3-deoxy-β-L-xylopyranoside (VI) (60% after recrystallization), m.p. 126·5—127·5°, $[\alpha]_D + 49°$, in agreement with the data reported by Williams[1] for the D-compound (m.p. 127—128°, $[\alpha]_D - 52°$), and which had identical i.r. and n.m.r. spectra with Williams' product. The method used by Williams,[1] however,



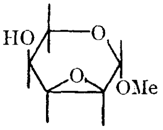
(I)



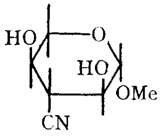
(II) R¹=H, R²=CN
(III) R¹=CN, R²=H



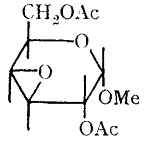
R=O[CH$_2$]$_4$O[CH$_2$]$_4$OH



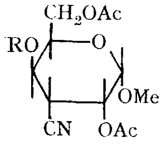
(V)



(VI)



(VII)



(VIII) R=H
(IX) R=Ac

---

† All new compounds had satisfactory elemental analyses; optical rotations are for chloroform solutions.

gave a mixture of two products, from which compound (VI) was isolated in 28% yield. Use of the reagent with methyl 2,6-di-*O*-acetyl-3,4-anhydro-α-D-galactopyranoside (VII) gave as the sole product, syrupy methyl 2,6-di-*O*-acetyl-3-cyano-3-deoxy-α-D-gulopyranoside (VIII) (23%), characterised as the 2,4,6-tri-*O*-acetyl derivative (IX), m.p. 95—96°, $[\alpha]_D + 44°$, the structure of which was established from its n.m.r. spectrum, $J_{1,2}$, $J_{2,3}$ 2·5 c./sec. This mode of ring-opening of (VII) is in agreement with that reported[4] for other nucleophiles.

It appears, therefore, that the aluminium triethyl–hydrogen cyanide in ether system is the best reagent for the synthesis of cyanohydrins from sugar epoxides.

Treatment of the cyano-sugar (II) (axial CN) with methanolic sodium methoxide caused epimerisation of the cyano-group (*cf.* ref. 1) to yield the *manno*-isomer (III) (equatorial CN), m.p. 166—167°, $[\alpha]_D - 11·3°$. At equilibrium the mixture contained (t.l.c.) only a trace of the *altro*-isomer (II). This is not unexpected in view of the strong 1,3-interaction shown, by *X*-ray study, to be present in (II).

As expected by analogy with the corresponding nitro-compounds,[5] the benzylidene group in compounds (II) and (III) was alkali labile.

We thank Imperial Chemical Industries (Pharmaceuticals Division) for financial support.

(*Received, August 2nd*, 1968; *Com.* 1055.)

---

[1] N. R. Williams, *Chem. Comm.*, 1967, 1012.

[2] W. Nagata, M. Yoshioka, and T. Okumura, *Tetrahedron Letters*, 1966, 847.

[3] F. H. Newth, *Quart. Rev.*, 1959, **13**, 30.

[4] A. Muller, *Ber.*, 1934, **67**, 421; 1935, **68**, 1094; M. Dahlgard, B. H. Chastain, and R. L. Hann, *J. Org. Chem.*, 1962, **27**, 929, 932; M. Dahlgard, *J. Org. Chem.*, 1965, **30**, 4352.

[5] H. H. Baer and W. Rank, *Canad. J. Chem.*, 1965, **43**, 3330.