General Lewis Acid Catalysis of Glycoside Anomerisation and *O*→*N*-Glycosyl Rearrangement

By DAVID THACKER and T. L. V. ULBRICHT

(*Twyford Laboratories, Elveden Road, London, N.W.*10)

THE mechanism of the synthesis of nucleosides and similar glycosides, from glycosyl halides and metal salts of heterocyclic bases containing the tautomeric group –NH–CO–, has been much studied in recent years.[1–3] In many cases the reaction involves an *O*→*N*-glycosyl rearrangement, catalysed by mercuric bromide or mercuric chloride. Various Lewis acids and other compounds have been tried as potential catalysts for this and related reactions, but apparently without success.[4–6] It has been reported that an *O*-glucoside of 5-nitro-2-pyridone does not rearrange to an *N*-glucoside, but yields an isomeric *O*-glucoside.[5] This interested us, because the ease of anomerisation of alkyl glycosides increases with an increase in the availability of electrons from the aglycone, and attempts to anomerise aromatic glycosides have generally failed.[7] We therefore reinvestigated the glucopyranosides of 5-nitro-2-pyridone (I), and established the anomeric configurations by ^{1}H n.m.r. spectroscopy. It was found that the *O*-glycoside obtained as the main product from the silver salt of (I) and acetobromoglucose is the β-anomer (II).

On treatment of (II) with mercuric bromide in toluene (heated under reflux), the α-*O*-glucoside (III) is produced, but contrary to an earlier report,[5] the β-*N*-glucoside (IV) (m.p. 99—100°, λ_{max} 300 mμ, ε 11,000) is also formed. The ^{1}H n.m.r. data for these compounds are given in the Table.

TABLE

^{1}H N.m.r. spectra of 5-nitro-2-pyridone O- *and* N-*glycosides measured on the glucopyranosyl acetates in* $CDCl_3$ *at 60 Mc./sec.*

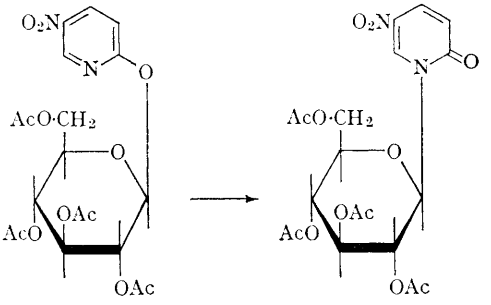
Glycoside	$H_{1'}$ (τ)	$J_{1'2'}$ (c./sec.)*
β-*O*-	3·73	8
α-*O*-	3·12	3·5
β-*N*-	3·73	8·5

* *C.f.*, B. Capon and D. Thacker, *Proc. Chem. Soc.*, 1964, 369.

The *N*-glucoside (IV) is also formed when (II) is treated with stannic chloride, titanium tetrachloride, or antimony pentachloride in benzene at room temperature, or zinc chloride or cadmium chloride in benzene heated under reflux. This gives some indication of the reactivity of these acids as catalysts, and it is worth noting that mercuric

bromide was found to be the best catalyst for obtaining the α-*O*-glucoside by anomerisation of the β-compound under conditions that gave little *N*-glucoside. With the other catalysts the anomerisation reaction could not be readily observed separately from the rearrangement and in all cases the reactions were found to be very dependent on the concentration of catalyst (and temperature).*

Treatment of the α-*O*-glucoside (III) with mercuric chloride or stannic chloride in benzene also yielded the β-*N*-glucoside, but no β-*O*-glucoside



(II) (IV)

could be detected. We have found that *O*→*N*-glycosyl rearrangement of the *O*-glucoside of *N*-acetylcytosine[4]† is also catalysed by stannic chloride. This is the first time that *O*→*N*-glycosyl rearrangements have been brought about by catalysts other than a mercuric halide.[8]

On the basis of these results it appears that both *O*→*N* rearrangement and anomerisation of glycosides of strongly electron-withdrawing aglycones are subject to general Lewis acid catalysis. Our failure to detect any α-*N*-glycosides in these reactions and the dependence of the reaction on concentration of acid (anomerisation with low concentrations, mainly rearrangement with high concentrations) suggests that two different mechanisms may be involved:

(i) Complex formation of the catalyst with the ring oxygen of the sugar, followed by ring-opening and ring-closing (anomerisation);

(ii) Complex formation of the catalyst with the glycosidic oxygen, formation of an ion-pair and neighbouring group participation by the 2-acyloxy-group[9] (stereospecific rearrangement).

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* The products were separated by preparative thin-layer chromatography on Silica GF_{254} (E. Merck A. G.) using ether as solvent. Rechromatography of the pure compounds did not cause anomerisation or rearrangement to take place.

† We have found that the product previously reported (ref. 4) contained some *N*-glucoside. The pure acetylated β-*O*-glucoside has m.p. 133—135°.

[1] T. L. V. Ulbricht, *Ann. Reports*, 1964, **61**, 448.
[2] F. Reisser and W. Pfleiderer, *Chem. Ber.*, 1966, **99**, 542, 547.
[3] H. G. Garg and T. L. V. Ulbricht, *J. Chem. Soc.* (*C*), 1967, 51.
[4] T. L. V. Ulbricht and G. T. Rogers, *J. Chem. Soc.*, 1965, 6123, 6130.
[5] G. Wagner and E. Fickweiler, *Arch. Pharm.*, 1965, **298**, 62.
[6] H. Zinner and K. Peseke, *Chem. Ber.*, 1965, **98**, 3508.
[7] R. U. Lemieux, *Adv. Carbohydrate Chem.*, 1954, **9**, 18.
[8] This was reported, in part, by the present authors at the Chemical Society meeting at Brighton in September 1966. Rearrangement of a pyrimidine *O*-glycoside with stannic chloride and silver perchlorate has since been briefly reported (G. Schmidt and J. Farkaš, *Coll. Czech. Chem. Comm.*, 1966, **31**, 4442).
[9] T. L. V. Ulbricht "Introduction to Nucleic Acids and Related Natural Products", Oldbourne Press, London, 1966, p. 32.