Glycosides of *N*-Hydroxy-*N*-arylamine Derivatives. Part 3.[1] Kinetic and Mechanistic Studies on the Degradation Reaction of *O*-Glycosides of *N*-Hydroxy-*N*-arylamines and their Acetohydroxamic Acids in Acidic and Alkaline Media

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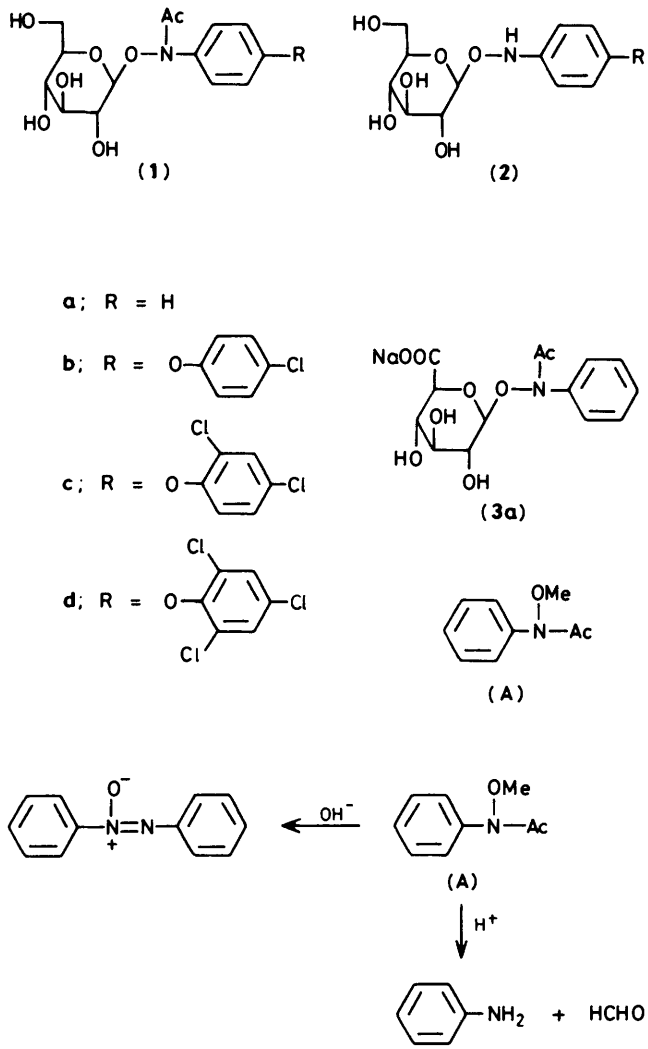
Good first-order kinetics of the degradation reaction of 1-[(*N*-acetyl-*N*-arylamino)oxy]-1-deoxy-β-D-glucopyranoses (**1a—d**), 1-(*N*-arylamino)oxy-1-deoxy-β-D-glucopyranose (**2a**) and sodium 1-[(*N*-acetyl-*N*-phenylamino)oxy]-1-deoxy-β-D-glucopyranuronate (**3a**) in aqueous acidic solutions have been observed. Compounds (**1a—d**) and (**3a**) were fairly stable in neutral solution, but in aqueous acidic solutions at 20 °C these compounds decomposed to the corresponding arylamino derivatives (**4a—d**) and D-gluconic acid (**5**) [D-glucaric acid in the case of the compound (**3a**)]. The compound (**2a**) decomposed *ca.* 7 400 times faster than compound (**1a**) to the same products (**4a**) and (**5**) in the same conditions. In an alkaline solution, compounds (**1a**)—(**3a**) gave the corresponding azoxybenzene. In the acid-catalysed redox degradation reaction, the hydrolysis of the *N*-acetyl group of compounds (**1a—d**) and (**3a**) is considered to be the rate-determining step. The effects of pH and additives on the reaction rate are reported. The mechanism of the acid-catalysed redox fission of the N–O linkage in the above *O*-glycosides is discussed.

In a previous paper,[2] the synthesis of a series of *O*-glucosides of *N*-hydroxy-*N*-arylacetamides (**1a—d**) and *N*-hydroxy-*N*-arylamines (**2a—d**) has been reported. Although several *O*-glucuronides of *N*-hydroxy-*N*-arylacetamides, which are thought to be carcinogens, have been obtained biosynthetically,[3–5] little is known about their chemical characteristics. The chemical reactivity of these compounds must be considered if one is to attempt to evaluate the effects of these compounds in biological systems. In the chemistry of *N*-hydroxy-*N*-arylamines and their mono- and di-acyl derivatives, N–O bond cleavage is well known in the mechanism of the Bamberger rearrangement[6–8] and Fries-type rearrangements.[9–12] These reactions are thought to proceed *via* a nitrenium intermediate, which is also postulated to be one of the active species capable of interacting covalently with nucleophilic sites of cellular macromolecules.

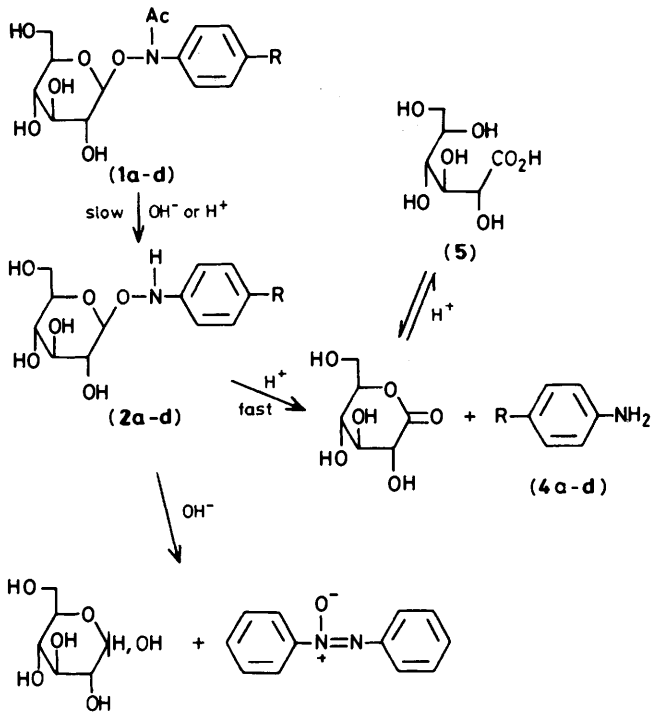
Compound (A), *N*-methoxyacetanilide,[13] a model for these glycosides, was briefly studied as regards the reactivity in both acidic and alkaline solutions. In alkaline solution, compound (A) was hydrolysed to give azoxybenzene, but in acidic solution aniline was detected. Compound (A) is positive to chromotropic acid,[14] a colour test for formaldehyde, and these facts prompted us to study the reactivity of the compounds (**1a—d**), (**2a**), and (**3a**) with particular regard to their degradation pathway in acidic solution.

Results

Product Studies.—The degradation products of the compound (**A**) in 0.1N-H_2SO_4 (pH 1.3) and 0.1N-NaOH [both contained EtOH; 20% (v/v)] were detected on silica gel t.l.c. Although the rates of the degradation reactions were very slow, aniline (**4a**) and azoxybenzene were detected in the acidic and alkaline solutions, respectively. Compound (**A**) was positive to chromotropic acid, indicating the formation of formaldehyde. In Scheme 1, the degradation products is shown. In contrast to compound (**A**), the glycosides (**1a—d**), (**2a**), and (**3a**) were more labile under both conditions. In 0.1N-NaOH, the u.v. spectrum of compound (**1a**) changed gradually to that of the authentic azoxybenzene. As shown in Scheme 2, this reaction probably involves intermediate (**2a**) formed through hydrolysis of the *N*-acetyl group in compound (**1a**). Since compound (**2a**) gave



Scheme 1.



Scheme 2.

azoxybenzene more rapidly, the hydrolysis of the *N*-acetyl group seemed to be rate determining. In 0.1N-H_2SO_4, absorption at 230 nm ($\lambda_{max.}$) gradually decreased but the pattern of the spectra maintained constant, which indicated that an intermediate or product having a low molar extinction coefficient was formed. However, when an equal volume of 0.1N-NaOH was added to the acidic solution after no change in the u.v. spectrum was observed, the spectrum changed to that of aniline (**4a**), with new maxima at 231 and 280 nm. To try to confirm the structure of the degradation products, degradation products of compound (**1a**) in D_2O–H_2SO_4 were next analysed by ^{13}C n.m.r. spectroscopy. After 30% conversion (determined by h.p.l.c.; see Experimental section), the spectrum showed signals due to the presence of acetic acid, aniline (**4a**), and D-gluconic acid (**5**), in addition to the signals attributed to the unchanged compound (**1a**). Assignment of ^{13}C signals was made by comparison of the chemical shifts with those of the authentic acetic acid, aniline, and D-gluconic acid measured in the same condition. Compounds (**1a**—**d**), (**2a**), and (**3a**) were positive to the Somogyi–Nelson reagent,[15] used for determination of reducing sugars, because of their lability in alkaline conditions to yield a free sugar. However, degradation products of these glycosides in the acidic solution were negative to the reagent, indicating the formation of D-gluconic acid and D-glucaric acid from compounds (**1a**) and (**3a**), respectively, through the redox cleavage of the N–O bond in their molecules. Although the latter compound was not characterized spectroscopically, its formation was further supported by an experiment using a β-glucuronidase assay.[16] D-Glucaric acid and its lactones are known as inhibitors[17] of β-glucuronidase, and the degradation products showed a significant inhibition in the above assay (data not shown). Final confirmation of products (**4a**) and (**5**) was achieved by conversion into toluene-*p*-sulphonamide and phenylhydrazide derivatives, respectively. These compounds had identical m.p.s and i.r. spectra with those of the corresponding synthetic compounds.

Table. First-order rate constant k_{obs} for compounds (**1a**—**d**), (**2a**), and (**3a**)

Compound	k_{obs}[a]/h^{-1}	Rel. k_{obs}
(**1a**)	2.31×10^{-2}	1.00
(**1b**)	2.26×10^{-2}	0.98
(**1c**)	2.21×10^{-2}	0.96
(**1d**)	2.23×10^{-2}	0.97
(**2a**)	1.71×10^{2}	7.40×10^{3}
(**3a**)	2.90×10^{-2}	1.26

[a] In 0.1N-H_2SO_4 containing 10% (v/v) EtOH; pH 1.3 at 20 °C.

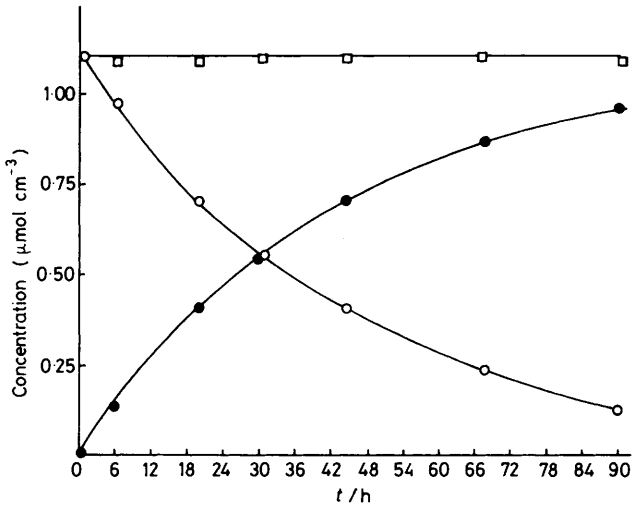


Figure 1. Time course of disappearance of compound (**1a**) and concomitant formation of aniline (**4a**) in 0.1N-H_2SO_4 (pH 1.3): ○, compound (**1a**); ●, aniline (**4a**); □, aggregate

Kinetic Studies.—When compounds (**1a**—**d**) were hydrolysed in 0.1N-H_2SO_4 (pH 1.3) at 20 °C, their disappearance and the concomitant formation of the corresponding arylamines (**4a**—**d**) were observed. The time course of the degradation of compound (**1a**) is shown in Figure 1. Upon h.p.l.c. analysis, no detectable intermediates or other products such as the *O*-glucosides of *o*-(or *p*-)hydroxyacetanilide and *o*-(or *p*-)aminophenol were observed. The reaction rates followed strictly first-order kinetics, and the observed first-order rate constants (k_{obs}) of compounds (**1a**—**d**), (**2a**), and (**3a**) are listed in the Table. Since in these conditions the corresponding *N*-hydroxy-*N*-arylacetamides and arylacetamides did not afford the corresponding arylamines (**4a**—**d**) these degradation reactions of compounds (**1a**—**d**) probably involve an intermediate, the *O*-glucoside of *N*-hydroxy-*N*-arylamines (**2a**—**d**) but these were not detected, and have only a transient existence, so that the rate-determining step is thought to be hydrolysis of the *N*-acetyl group in compounds (**1a**—**d**) as shown in Scheme 2. This is supported by the finding that the value of k_{obs} of compound (**2a**) is *ca.* 7 400 times larger than that of compound (**1a**). This consideration could be applicable to the case of compound (**3a**).

Effect of pH.—The rate constants k_{obs} for the degradation of compound (**1a**) was measured in aqueous H_2SO_4 of various concentrations at 20 °C (Figure 2). The rate constant k_{obs} increased with increasing $[H^+]$; this is characteristic for hydrolysis reactions catalysed by H^+. The rate contant is given by equation (i). However, no detectable degradation reaction

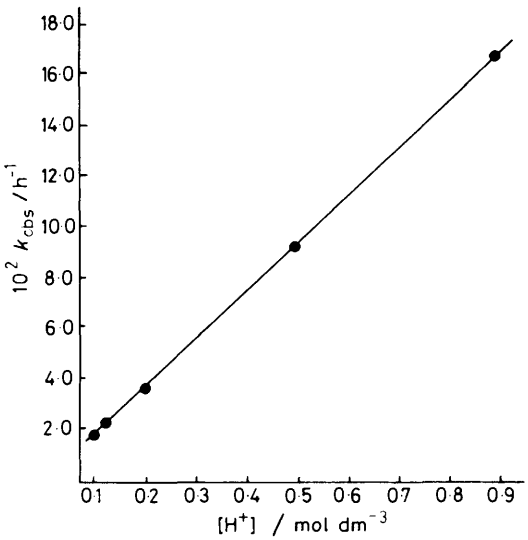


Figure 2. Plot of observed rate constant *versus* [H^+] at 20 °C and [(**1a**)] 10^{-3}M

$$k_{obs} = k^{H}[H^+] + k^{H_2O}[H_2O] + k^{OH}[OH^-] \quad (i)$$

was observed in neutral medium (0.1M-potassium phosphate buffer, pH 6.9). Therefore, the observed rate constant k_{obs} in acidic media is given by equation (ii).

$$k_{obs} = k^{H}[H^+] \quad (ii)$$

As shown in Figure 2, the linear plot between the rate constant k_{obs} and [H^+] indicated that the degradation rate is first-order with respect to H^+ in the range of [H^+] examined. When the reaction was carried out in aqueous HCl solutions (0.1, 0.2, and 1.0N) instead of aqueous H_2SO_4, the rate constant k_{obs} at a given [H^+] was the same as the value obtained in H_2SO_4 solution at the same [H^+], and *o*-(or *p*-)chloroaniline, one of the Bamberger rearrangement products of *N*-phenylhydroxylamine,[6] was not detected.

Effect of Additives.—In the consecutive mechanism of the degradation reaction (Scheme 2), the initial step could be hydrolysis of the *N*-acetyl group. However, little mechanistic information for the second step, a redox cleavage of the N–O bond linkage in the intermediates (**2a**—**d**), is available. So, the degradation reactions of compound (**1a**) in 0.1N-H_2SO_4 (pH 1.3) at 20 °C were next examined in the presence of additives such as D-glucose, *N*-phenylhydroxylamine, phenol, butylated hydroxytoluene (BHT), $FeSO_4$, and $Fe_2(SO_4)_3$. The rate of degradation of compound (**1a**) was not affected by the additives and no compounds other than aniline (**4a**) were detected. *N*-Phenylhydroxylamine did not afford aniline (**4a**) under the same conditions either in the presence or in the absence of D-glucose (10 equiv.).

Measurement of Optical Rotation.—The change of the optical rotation of the degradation reaction of compound (**1a**) was next monitored. Through the reaction, a good linear relationship between the observed $[\alpha]_D^{20}$ values and the percentage of conversion (determined by h.p.l.c. analysis) was obtained and there is good agreement between the observed and the calculated $[\alpha]_D^{20}$ values according to equation (iii), where −55.2° and +7.5° are the values of the optical rotation of compound (**1a**) and D-gluconic acid (equilibrated with D-glucono-1,5-lactone in 0.1N-H_2SO_4), respectively, and *Y* is conversion percentage.

$$\text{calc. } [\alpha]_D^{20} = \frac{-55.2°(100 - Y) + 7.5°Y}{100} \quad (iii)$$

Discussion

The degradation reaction of compounds (**1a**—**d**) in both acidic and alkaline solution was thought to proceed *via* the same intermediates (**2a**—**d**) formed through the hydrolysis of the *N*-acetyl group in compounds (**1a**—**d**) because the hydroxamic acids were hydrolysed under both conditions.[18] In alkaline solution, hydrolytical cleavage of the *N*-acetyl group followed by that of the glucosidic bond occurred to give the corresponding hydroxylamines which were then converted into azoxy compounds as described by Irving.[19]

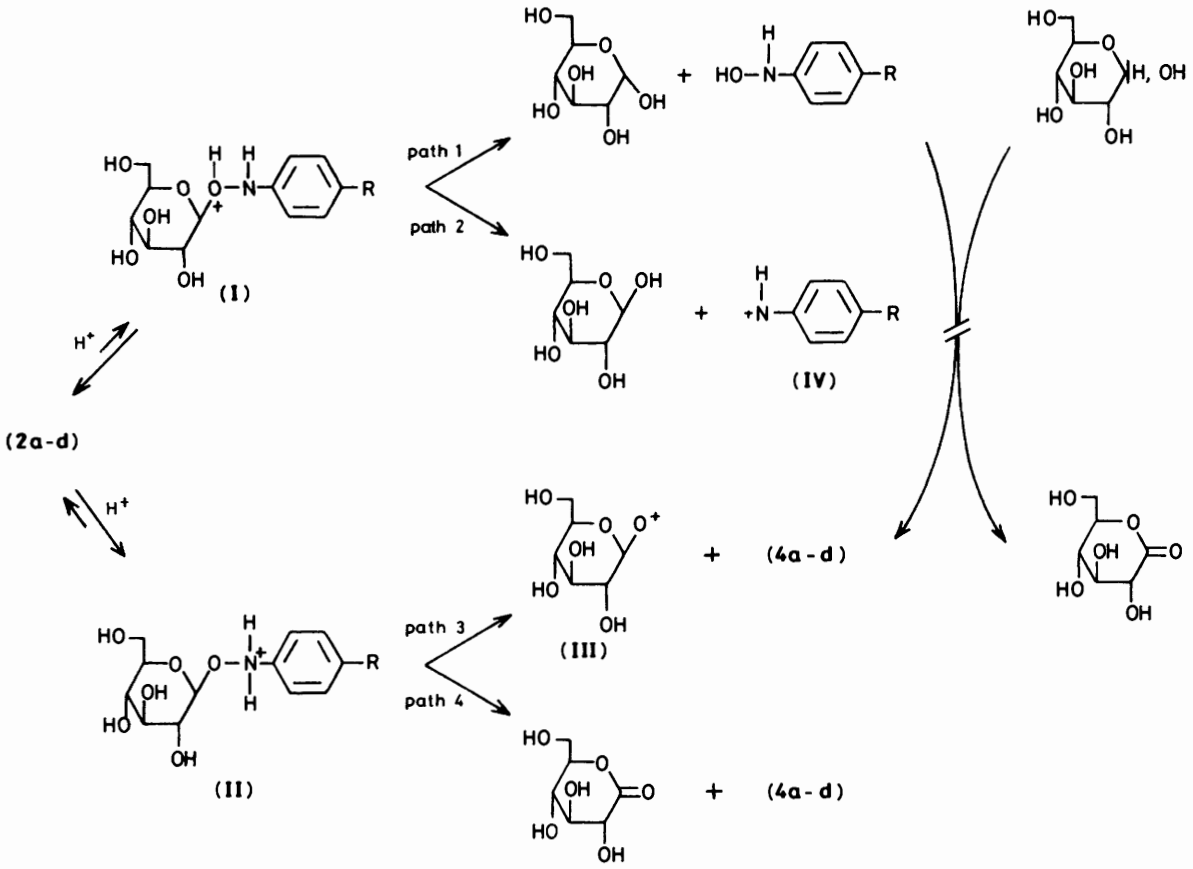
In acidic solution, the intermediates (**2a**—**d**) were converted into the corresponding arylamines (**4a**—**d**) and D-gluconic acid (**5**) through redox fission of the N–O linkage (Scheme 2).

This acid-catalysed N–O bond fission of compounds (**1a**—**d**), (**2a**), and (**3a**) is thought to be different from Bamberger [6-8] and Fries-like rearrangements[9-12] in the following points: (i) this reaction is intramolecular, but the others are reported to be intermolecular rearrangements and (ii) it affords both reduced and oxidized products, but the others gave a product with both the reduced and oxidized sites in the molecule.

Reaction Mechanism.—As shown in Scheme 3, four pathways, 1—4, are proposed. In the Bamberger rearrangement of *N*-phenylhydroxylamine, the active species is reported[7] to be the *O*-protonated compound $PhNHO^+H_2$ at pH < 1.0. Paths 1 and 2, intermolecular redox mechanisms, in which the *O*-protonated intermediate (**I**) participates, are easily excluded by the following reasons: (i) the rate of the degradation of compound (**2a**) followed first-order kinetics, (ii) the addition of D-glucose and *N*-phenylhydroxylamine does not affect the rate constant, (iii) *N*-phenylhydroxylamine does not afford aniline (**4a**) under the same conditions in either the presence or the absence of D-glucose, and (iv) no compound derived from Bamberger-type rearrangement is detected. Since it is likely that *N*-protonation is more extensive because of the pK_a value[7] of *N*-phenylhydroxylamine, paths 3 and 4 seem to be reasonable. The intermediate (**II**), an *N*-protonated form, could afford the corresponding arylamines (**4a**—**d**) through either a non-concerted (path 3) or a concerted (path 4) mechanism. In path 3, it is thought that the intermediate (**III**), an oxenium ion, can react with nucleophiles. No formation of the *O*-glucoside of *o*- (or *p*-)hydroxyarylamine is explained by considering that arylamines (**4a**—**d**) are present in the protonated form. However, when external nucleophiles such as phenol and BHT were added to the reaction mixture, electrophilic substitution products were not detected upon h.p.l.c. analysis. A radical mechanism is excluded by the finding that the rate constants k_{obs} are not affected in the presence of phenol and BHT, as radical scavengers, and Fe^{2+} and Fe^{3+}, as radical mediators. From these facts, path 4, an intramolecular concerted mechanism, would be the most reasonable pathway though the possibility of path 3 is not excluded completely.

The *O*-glucuronide of *N*-hydroxyacetanilide has been reported[20] to be negative to the naphthoresorcinol reagent,[21] a colour reaction based on the formation of furfural derivatives under acidic conditions. This is because of acid-catalysed redox fission of the N–O linkage in the molecule.

Recently, Greci[22] reported the acid-catalysed disproportionation of a nitroxide through a protonated compound like the intermediate (**II**). Corbett[23] reported that *N*-hydroxy-4-(*NN*-dimethylamino)formanilide was reduced to the corresponding formanilide derivative by glyoxylic acid or formaldehyde. Mulder *et al.*[24] reported that the *O*-glucuronide of *N*-hydroxyphenacetin in neutral, aqueous solution gave phenacetin and



Scheme 3.

an oxidized product of D-glucuronic acid through intramolecular rearrangement, though the latter compound was not characterized. On the other hand, in this study, the glycosides (**1a**—**d**) and (**3a**) gave the corresponding amino derivatives (**4a**—**d**) but not the corresponding acetamide derivatives in acidic solution. These differences in the reactivity of *N*-hydroxy-*N*-arylacetamide derivatives seem to be due to the *N*-substituted aryl group, which has a strong effect not only on the rate but also on the direction of reaction. The relationship between reactivity and structure in the *N*-substituted aromatic compounds as well as sugar moieties, and the effect of pH on the reactivity, must be further investigated. Although there was no significant effect of the chloro-substituted phenoxy group on the rate of the degradation reaction of compounds (**1a**—**d**) at the pH examined (Table), the glucuronide (**3a**) decomposed faster than the corresponding glucoside (**1a**), which indicated that the carboxy group in the former compound facilitated the hydrolysis of the *N*-acetyl group in the molecule.

As shown in a previous paper,[2] compound (**2a**) was shown to decompose to aniline (**4a**) and azoxybenzene through the same intermediate, the corresponding *N*-deacetylated derivative, in neutral solution. In the *N*-deacetylated compounds (**2a**—**d**), the reactivity is probably affected by the pK_a value of the corresponding hydroxylamino derivatives.

Experimental

General experimental directions are given in Part 1.[2] ^{13}C N.m.r. spectra were recorded on a JEOL JNM-FX100 spectrometer using sodium 4,4-dimethyl-4-silapentane-1-sulphonate (DSS) as internal standard. H.p.l.c. analyses were made with a Shimadzu LC-5A system using a reverse-phase column, Zorbax C8 (4.6 × 250 mm) (Dupont).

Materials.—*O*-Glucosides (**1a**—**d**) and (**2a**) were synthesized by the procedure reported in a previous paper.[2] *N*-Methoxyacetanilide[13] was prepared from *N*-hydroxyacetanilide and methyl iodide according to the reported procedure.[25] β-D-Glucopyranosides of *o*-acetamidophenol,[26] *p*-acetamidophenol,[26] *o*-aminophenol,[27] and *p*-aminophenol[27] were prepared by the reported procedures. Sodium 1-deoxy-1-[(*N*-acetyl-*N*-phenylamino)oxy]-β-D-glucopyranuronate (**3a**) was obtained biosynthetically according to the method described by Fishman.[20] Isolation was simplified by using an XAD-4 column, m.p. 163 °C (decomp.) (from water–acetone) [lit.,[20] 158 °C (decomp.)] (Found: C, 45.9; H, 4.9; N, 3.9. Calc. for $C_{14}H_{16}O_8NNa{\cdot}H_2O$: C, 45.8; H, 4.9; N, 3.8%). The structure was confirmed by i.r. and ^1H n.m.r. spectra.

Identification of the Degradation Products of the Compound (**1a**).—A solution of compound (**1a**) (82 mg) in 0.1N-H_2SO_4 (200 ml) was allowed to stand at 37 °C. After 4 d (the reaction was complete), the mixture was neutralized with 0.2N-barium hydroxide. Barium sulphate was filtered off and the filtrate was extracted with ether (50 ml × 3). The ether extracts were combined and evaporated *in vacuo*. The residue was treated with toluene-*p*-sulphonyl chloride (110 mg) in pyridine (0.5 ml) to give toluene-*p*-sulphonanilide as sole product; m.p. and mixed m.p. 100—102 °C (from ethyl acetate–n-hexane) (lit.,[28] 103 °C); $\lambda_{max.}$(KBr) 3 250, 1 660, 1 340, and 1 115 cm^{-1}. The

aqueous layer after ether extraction was concentrated *in vacuo* to a small portion (*ca.* 20 ml) and to which Dowex 50W-X8 (H^+ form) (100 mg) was added and the mixture was stirred for 15 min. After filtration, the filtrate was concentrated *in vacuo* to *ca.* 2 ml, and then phenylhydrazine (0.1 ml) and acetic acid (0.05 ml) were added and the mixture was warmed at *ca.* 90 °C for 2 h to give the phenylhydrazide of D-gluconic acid (**5**); m.p. and mixed m.p. 199 °C (decomp.) (from water) (lit.,[29] 200 °C); $\lambda_{max.}$(KBr) 3 400, 3 260, 2 950, 1 650, 1 600, 1 500, 1 085, and 1 035 cm^{-1}.

Degradation of O-*Glucosides* (**1a—d**) *in Aqueous Sulphuric Acid Solution.*—(A) *H.p.l.c. analysis.* A solution of *O*-glucoside (**1a**) in aqueous sulphuric acid was incubated at 20 °C. When a series of *O*-glucosides (**1a—d**) was hydrolysed under the same conditions, an aqueous sulphuric acid containing 10% (v/v) ethanol was used. At the assay, a portion (0.4 ml) of the hydrolysis mixture was diluted with CH_3CN (1.6 ml) and Dowex 1W-X8 (hydrogencarbonate form) (50 mg, 0.16 mequiv.) was added. After mixing, portions (10 μl) were injected onto a Zorbax C8 column using CH_3CN–H_2O as eluant. The solvent flow rate was 1.0 and 2.0 ml min^{-1} in the case of compounds (**1a**) and (**1b—d**), respectively. Detection was made at 240 nm. Quantitative calculations were made on the basis of peak areas compared with those generated by known amounts of the authentic standard. In this condition, the retention times for *O*-glucosides (**1a—d**) were 2.40, 1.51, 1.63, and 1.73 min, respectively. The retention times for the corresponding amino derivatives (**4a—d**) were 4.90, 5.75, 7.41, and 8.95 min, respectively.

(B) *Measurement of specific rotation.* A solution of *O*-glucoside (**1a**) (*c* 0.54M) in 0.1N-H_2SO_4 was hydrolysed at 37 °C. Each time when the specific rotation was measured, an aliquot portion of the mixture was analysed by h.p.l.c. as described above. Under the same conditions, the specific rotation of D-glucono-1,5-lactone were also measured immediately after its dissolution, during mutarotation, and when mutarotation was complete.

(C) *Measurement of* ^{13}C *n.m.r. spectra.* *O*-Glucoside (**1a**) (30 mg) was dissolved in D_2O (0.25 ml) containing DSS (7 mg). ^{13}C N.m.r. spectra were recorded in this time, and after addition of 1N-H_2SO_4 (25 μl). Under the acidic conditions, ^{13}C n.m.r. spectra of aniline (**4a**), D-glucono-1,5-lactone,[30,31] and D-gluconic acid were also measured.

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Received 2nd July 1984; *Paper* 4/1137